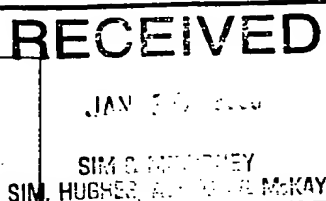


PATENT COOPERATION TREATY

From the:
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



PCT

To:
BARTOSZEWICZ, Lola A.
Sim & McBurney
330 University Avenue
6th Floor
Toronto, Ontario M5G 1R7
CANADA

WRITTEN OPINION

(PCT Rule 66)

| | |
|---|---|
| Date of mailing (day/month/year) 05.01.00 | |
| Applicant's or agent's file reference 7479-23 LAB | REPLY DUE within 3 month(s) from the above date of mailing |
| International application No. PCT/CA98/00046 | International filing date (day/month/year) 29/01/1998 |
| Priority date (day/month/year) 29/01/1998 | |
| International Patent Classification (IPC) or both national classification and IPC A61L27/00 | |
| Applicant MILLENIUM BIOLOGIX, INC. et al. | |

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain document cited
 - VII ☐ Certain defects in the international application
 - VIII ☒ Certain observations on the international application
3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: **29/05/2000.**

| | |
|---|---|
| Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer / Examiner Smetankine, L <hr/> Formalities officer (incl. extension of time limits) Senkel, H Telephone No. +49 89 2399 8071 |
|---|---|



PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

| | | |
|---|---|---|
| Applicant's or agent's file reference 7479-23 LAB | FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below. | |
| International application No. PCT/CA 98/ 00046 | International filing date (day/month/year) 29/01/1998 | (Earliest) Priority Date (day/month/year) |
| Applicant MILLENIUM BIOLOGIX, INC. et al. | | |

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. ☒ **Certain claims were found unsearchable** (see Box I).
2. ☐ **Unity of invention is lacking** (see Box II).
3. ☐ The international application contains disclosure of a **nucleotide and/or amino acid sequence listing** and the international search was carried out on the basis of the sequence listing
 - ☐ filed with the international application.
 - ☐ furnished by the applicant separately from the international application,
 - ☐ but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - ☐ Transcribed by this Authority
4. With regard to the **title**, ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:
5. With regard to the **abstract**, ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the **drawings** to be published with the abstract is:
 Figure No. _____ ☐ as suggested by the applicant. ☒ None of the figures.
☐ because the applicant failed to suggest a figure.
☐ because this figure better characterizes the invention.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 98/00046

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 43-52
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 43-52
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition (Rule 39.1(iv) PCT).
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

REPLACED BY
PCT/CA/98/00046

PATENT COOPERATION TREATY

PCT

REC'D 15 MAY 2000

WIPO

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

| | | |
|---|--|--|
| Applicant's or agent's file reference 7479-23 LAB | See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416) FOR FURTHER ACTION | |
| International application No. PCT/CA98/00046 | International filing date (day/month/year) 29/01/1998 | Priority date (day/month/year) {29/01/1998} |
| International Patent Classification (IPC) or national classification and IPC A61L27/00 | | |
| Applicant MILLENIUM BIOLOGIX, INC. et al. | | |

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.



2. This REPORT consists of a total of 6 sheets, including this cover sheet.

- ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☒ Certain observations on the international application

| | |
|---|--|
| Date of submission of the demand 30/08/1999 | Date of completion of this report 11.05.00 |
| Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465 | Authorized officer Smetankine, L Telephone No. +49 89 2399 8466  |

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA98/00046

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-35 as originally filed

Claims, No.:

10 (part), 11-52 as originally filed

1-9, 10 (part) as received on 06/04/2000 with letter of 04/04/2000

Drawings, sheets:

1/19-19/19 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application.
☒ claims Nos. 1,2,5-18,21-48,52.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA98/00046

because:

- ☒ the said international application, or the said claims Nos. 35-37,43-52 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1,2,5-18,21-48,52 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | | |
|-------------------------------|------|--------|-----------------|
| Novelty (N) | Yes: | Claims | 4 |
| | No: | Claims | 3,19,20,49-51 |
| Inventive step (IS) | Yes: | Claims | |
| | No: | Claims | 3,4,19,20,49-51 |
| Industrial applicability (IA) | Yes: | Claims | 3,4,19,20,49-51 |
| | No: | Claims | |

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA98/00046

POINT III:

1. Claims 37 to 39, 43 o 52 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Certain claims concerned "per se" compound which is defined by its ingredients or elements. Insofar that one ingredient is not defined, the compound could not be identified for several reasons: first it is not clear in what physical form is the biomaterial: crystal, amorphous ? second- what element from calcium, oxygen or phosphorus is substituted by " said element" and third for a skilled person it is not clear the element which could correspond to this definition: the description gave any element having an ionic radius of 0.1 to 1.1 Angstrom- for instance table 2 page 32 specify some "ionic **crystal** Radius" or "**Effective** ionic radius" and in these cases only for coordination numbers 4,6 or 8 (se page 17 line 15) in crystals! Therefore claim 1 does not sem to be clear and also is does not seem to be supported by the description. The same apply to claims 2,5-18, 21 to 48,52.

Further the "additive" is not defined in claim 16 nor in claim 17 and 52: according to page 20 line 31 only "polymers or microfibers" are specified. Thus these terms should be used instead. Thus these claims do not seem to meet the requirements concerning clarity and support by the description.

POINT V:

1. Novelty:

J. of the Australian Ceramic Society, vol.29, n° 1/02, 1993, pp.71-80 (2) - see page 71 last paragraph (last line), describes the bioresorbable biomaterial, subject - matter of claims 3, thus this claim seem to lack novelty.

WO - A - 91/17965 (3) - see abstract, page 5 paragraph 1 to paragraph 3, claims

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA98/00046

1,6-10, describes the biomaterial compound, wherein the substitution element is silicon, thus claims 3,19,20,49-51 seem to lack novelty.

Solid State Ionics, vol.95, n°1/02, 1995,pp.121-129 (4) - see abstract, describes natural silicate - containing apatites.

US - A - 4 503 157 (5) - see abstract, column 4 line 66 to column 5 line 17, column 10 example 2 , describes biocompatible apatite - mineral fibre composite.

WO - A - 95/32008 (6) - see abstract, page 11 lines 1-15, page 23 lines 7 to 22, page 30 lines 21-28, describes biomaterial implants based on hydroxyapatite.

FR - A - 2 664 501 (7) - see abstract, page 2 line 22 to page 3 line 8, claims 1,4,5 and 10, describes implant material based on phosphate calcium and collagen composite.

2. Inventive step:

It seem obvious for a skilled person to use a boron substitute in the biomaterial of the present application, further this material does not seem to bring advantages over the materials cited in the state of the art. The closest document seems to be (3) which brings biomaterial subject - matter of the present application, thus claims 3,4,19,20, 49 to 51 seem to lack inventive step.

3. Therapeutical treatment:

For the assessment of the present claims 35-37,43-52 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA98/00046

POINT VIII:

- 1) see §2 of the above point III
- 2) the last sentence in page 7 lines 28 to 30, is speculative and therefore it should be deleted.

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/CA 98/00046

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61L27/00 C01B33/24 C01B35/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61L C01B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|--|--|
| E | <p>GB 2 316 940 A (QUEEN MARY & WESTFIELD COLLEGE ; INST DE ENGENHARIA BIOMEDICA (PT)) 11 March 1998</p> <p>see abstract see page 2, line 16 - page 4, line 4 --- -/--</p> | <p>1-3, 7-16, 19-22, 30-35, 37-39, 43, 44, 48-52</p> |

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

2 October 1998

Date of mailing of the international search report

12/10/1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Heck, G

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 98/00046

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|----------|---|---|
| X | <p>RUYS A J: "SILICON-DOPED HYDROXYAPATITE" JOURNAL OF THE AUSTRALIAN CERAMIC SOCIETY, vol. 29, no. 1/02, 1993, pages 71-80, XP002048629</p> <p>see page 71, paragraph 1 - page 72, paragraph 5</p> | <p>1-3, 7-16, 19-22, 30-35, 37-39, 43,44, 48-52</p> |
| X | <p>WO 91 17965 A (UNIV FLORIDA) 28 November 1991</p> <p>see page 5, paragraph 1 - paragraph 3 see claims 1,6-10</p> | <p>1-3, 7-16, 19-25, 28-35, 37-39, 43,44, 48-52</p> |
| Y | <p>BOYER L ET AL: "SYNTHESIS OF PHOSPHATE - SILICATE APATITES AT ATMOSPHERIC PRESSURE" SOLID STATE IONICS, vol. 95, no. 1/02, 30 November 1995, pages 121-129, XP002048976 see abstract</p> | <p>5,6,14, 17,18, 26,27, 36, 40-42, 46,47</p> |
| Y | <p>US 4 503 157 A (HATAHIRA SEIICHI) 5 March 1985 see abstract see column 4, line 66 - column 5, line 17 see example 2</p> | <p>17,18</p> |
| Y | <p>WO 95 32008 A (IMPLICO BV ;RIPAMONTI UGO (ZA); KIRKBRIDE ANTHONY NIGEL (ZA)) 30 November 1995 see page 11, line 1 - line 15 see page 30, line 21 - line 28; examples 3,4</p> | <p>26,27, 40-42, 46,47</p> |
| Y | <p>FR 2 664 501 A (OSTEAL MEDICAL LABORATOIRES) 17 January 1992 see page 3, line 4 - line 8 see claims 1,4,5,10</p> | <p>36,40-42</p> |

INTERNATIONAL SEARCH REPORT

International application No.

PCT/CA 98/ 00046

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 43-52
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 43-52
are directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition (Rule 39.1(iv) PCT).
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 98/00046

| Patent document cited in search report | | Publication date | Patent family member(s) | Publication date |
|---|---|---------------------|---|--|
| GB 2316940 | A | 11-03-1998 | AU 4026397 A WO 9808773 A | 19-03-1998 05-03-1998 |
| WO 9117965 | A | 28-11-1991 | US 5074916 A | 24-12-1991 |
| US 4503157 | A | 05-03-1985 | JP 1377234 C JP 59057970 A JP 61041876 B JP 1481334 C JP 59057971 A JP 63027308 B DE 3375298 A EP 0104640 A GB 2130187 A, B | 08-05-1987 03-04-1984 18-09-1986 10-02-1989 03-04-1984 02-06-1988 18-02-1988 04-04-1984 31-05-1984 |
| WO 9532008 | A | 30-11-1995 | AU 694943 B AU 2456295 A DE 19581649 T EP 0760687 A GB 2302656 A, B JP 10500343 T ZA 9504217 A | 06-08-1998 18-12-1995 07-05-1997 12-03-1997 29-01-1997 13-01-1998 22-01-1996 |
| FR 2664501 | A | 17-01-1992 | NONE | |

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Please Quote 7479-23 LAB
Our ref.

Your ref.

Writer's Ext. 200
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By Facsimile – Confirmation Copy by Courier

April 4, 2000

Attention: Examiner L. Smetankine
European Patent Office
D-80298 Munich

Dear Sir:

Re: PCT Application Serial No. PCT/CA98/00046
 Applicant : Millenium Biologix Inc. et al
 Title : A Synthetic Biomaterial Compound

This is responsive to the Written Opinion dated January 5, 2000. The Examiner had indicated in Point III of the report that claims 1, 2, 5-18, 21-48 and 52 directed to a compound, could not be identified due to the fact that "element" was not specifically identified. Furthermore, claims 16, 17 and 52 were directed to unidentifiable compounds because the term "additive" was not specifically defined. The Applicant respectfully disagrees with the Examiner. The term "element" as used in the claims is adequately described in the claims and thus clearly understood by one skilled in the art. One skilled in the art readily understands that "element" refers to those elements of nature disclosed in the periodic table of elements. In claim 1 for example, element is further defined as having an ionic radius of 0.1 to 1.1 Å. Ionic radius is defined in the description at page 17, lines 13 to 20. Furthermore, Table 2 lists the effective ionic radius and ionic crystal radius for a selection of various elements with a supporting reference listed therein. Therefore, claims 1, 2, 5-18, 21-48 and 52 clearly define the biomaterial compound.

With respect to the term "additive" not being defined in claim 16, 17 or 52, we would again disagree with the Examiner. One skilled in the art with a reading of the description would readily comprehend the meaning of the term as used in these claims. "Additive" is specifically defined in the description on page 20, lines 30 to 36. Thus, the claims need not be needlessly overly restricted since they are readily understandable by one skilled in the art.

The Examiner rejected claim 3 as being previously taught and disclosed in the J. of the Australian Ceramic Society 1993 (Ruys). While the Applicant disagrees with the Examiner enclosed herewith is page 36 of the claims in which claim 1 has been amended to recite "A bioresorbable biomaterial compound ...". This amendment was made to better distinguish the presently claimed invention from that taught by Ruys. Support for such amendment can be found throughout the description for example, at page 1, line 19 and at page 4, lines 19-20 and 33-35. The presently claimed compound is well described on page 8 to be bioactive and allow for support of both osteoclast and osteoblast activity such that the material can be incorporated into natural bone.

Ruys teaches the formation of silicon-substituted hydroxyapatite in order to further enhance the biological properties of this well documented biomineral. Substitution of ions in hydroxyapatite is known through the analysis of such events in natural bone. While this may be an improvement to conventional hydroxyapatite, it fundamentally does not address remodeling which is a critical aspect of the maintenance of the skeleton.

The presently claimed invention is directed to the development of a completely new biomaterial, a silicon stabilized tricalcium phosphate (SiTCP). This material not only performs well from the perspective of bone ingrowth but has a key advantage over conventional synthetic bone biomaterials, including silicon substituted hydroxyapatite, in that this new compound is able to participate in the complete cycle of bone remodeling. This cycle fundamentally involves the orderly removal of old or damaged bone by the resorptive activity of osteoclast bone cells followed by the deposition of new natural bone by the mineralizing activity of osteoblasts. This is an extremely important consideration in assessing the biological performance of an implant, since the ability to participate in remodeling underpins the concept of an evolving bioactive material where the implant is progressively replaced through natural cell mechanisms. The logical extension of this concept is the therapeutic objective of having the synthetic compound completely remodeled such that it is no longer present as a source of potential complications later in the life of the patient. This true bioactivity, as described and claimed in the present invention, is not contemplated or taught in the Ruys paper.

Furthermore Ruys, does not address the remodeling activity continually underway throughout the skeleton and its effect on the stability and longevity of implanted synthetic materials. In fact, Ruys describes material processing objectives that are to the contrary with emphasis on a processing route selected "in order to avoid formation of biodegradable TCP". This is understandable since conventional TCP is recognized to exhibit uncontrolled degradation by random dissolution when implanted in the body. As a result of this degradation, the implanted material demonstrates inconsistent biological and structural performance at the implant site. Importantly, the claimed biomaterial of the present invention eliminates this problem through the use of a stabilized composition that does not suffer from random dissolution at physiological pH. This chemical stability has been achieved in combination with the ability of bone cells to naturally remodel the implant as part of the healing process.

To summarize, Ruys does not teach the invention as currently claimed in claim 3 which is dependent upon newly amended claim 1.

Claims 3, 19, 20 and 49-51 were also rejected as previously taught and disclosed by WO 91/17965. This international patent application is directed to sol-gel processing techniques producing bioactive glass compositions comprising 60-86% silicon dioxide, 4-33% calcium oxide and 3-15% phosphate. This work teaches a bioactive amorphous glass in which minor proportions of CaO and P₂O₅ are present in a predominantly SiO₂ material. The only link with calcium phosphate compounds is the ability to promote the natural formation of hydroxyapatite in apposition to the material when exposed to body fluids.

Furthermore, this application does not address element substitution in synthetic calcium phosphate compounds nor the critical role of remodeling in the maintenance of the skeleton. In fact, the objective of the work is to generate initial tissue bonding to the implant on a chemical level without reference to the activity of bone cells in the biological response of the host.

Hence, apart from the use of a sol-gel processing route, which in itself is not novel, this work is distinctly separate and independent of the work of the present invention. For these reasons, WO 91/17965 does not teach or suggest the presently claimed invention as claimed in claims 3, 19, 20 and 49-51. This published international application certainly does not teach the specific formulae as recited in these claims.

The Examiner asserts that it would be obvious for a skilled person to use a boron substitute in the biomaterial of the present application. Also, the Examiner states that the present material does not bring any advantages over the materials in the cited art. The presently claimed invention is directed to a biomaterial compound which has a distinctive microporous structure and permits for active resorption of the compound by osteoclasts as well as deposition of bone matrix by osteoblasts. As such, the compound is both bioactive and bioresorbable and can be used for *in vivo*, *in vitro* and *ex vivo* applications pertaining to bone growth and remodeling. The compound functions like natural bone in that it is remodeled *in vivo*. The characterization of the present compound was a difficult and complicated process and resulted in the knowledge that the compound was a stabilized new compound having a specific structure and formula which provided for its unique characteristics in the normal functioning of both osteoclasts and osteoblasts and thus use in several different types of bone applications. No prior art has taught or suggested such a novel compound that is remodelled like natural bone *in vivo*.

The journal article Solid State Ionics 95 (1997) 121-129 discusses substitutional reactions involving lanthanide elements in calcium phosphate compounds. There is no reference to the deliberate use of silicon as a substitutional element in biomaterials where the presence of silicon improves biological behavior. Indeed, this work is directed toward the "preparation of materials suitable for use as high performance matrices for long-lived radioactive wastes". Clearly, this work does not address the compositions of the present invention nor the related biological functionality or medical application.

US 4,503,157 patent is entirely focused on a structurally reinforced material that utilizes fibers to provide strength and toughness in an otherwise brittle bioceramic. The objective of the work is to utilize a "reinforcing mineral fiber" to address "insufficient mechanical properties". While silicon is described, it is only in the context of silicon fibers where the material is active on a structural rather than chemical or physiological level. Furthermore, the issue of the specific biological behavior of these reinforced biomaterials following implantation is simply not addressed.

As is also evident in this cited patent, the selection of the reinforcement technique is complicated by a series of high temperature processing issues that have the potential to degrade the introduced strengthening agents. As a result, no one reinforcing technique is universally applicable to conventional bioceramics.

Claim 16 of the present invention relates to the use of an additive that increases the mechanical strength and toughness of the new silicon stabilized bioresorbable biomaterial, both alone and in combination, as described in claims 1 – 10. Due to the unique properties of this new compound, the selection of appropriate strength and toughening agents and related processing techniques are not obvious.

WO-A-95/32008 discloses the preparation of macro-porous hydroxyapatite implants for bone reconstruction. The key focus of the application is the macro geometry of the implant. No particular material composition is identified other than conventional bioceramics with known chemical properties. Furthermore, only bone ingrowth is discussed without reference to any remodeling of the implant. This prior art is distinctly separate and independent of the present invention and does not suggest the present claims.

FR 2 664 501 discloses a multi-component implant configuration that includes metallic, ceramic and organic constituents. There is no discussion or suggestion of substituted calcium phosphate bioresorbable biomaterials nor the role of such materials in the biological performance of the implant.

None of the above noted cited references discloses or suggest the present compound where for example, boron is used to substitute part of the calcium, oxygen or phosphorous. Furthermore, none of the references specifically suggest the compounds of claims 19, 20 or 49-51. As such these claims are unobviousness in view of the cited art.

Claim 7 has been amended to delete the term "phosphate". As such, claims 7 and 15 are clear. New page 36 enclosed herewith has this amendment incorporated therein in claim 7.

With respect to the statement on page 7, lines 28 to 30, such a statement is allowable in certain national phase countries and therefore will presently be maintained.

In view of the above submissions, favourable reconsideration is requested.

Very truly yours,
SIM & McBURNEY

Lola A. Bartoszewicz, Ph.D.

LAB/ca
Encls: revised page 36

WRITTEN OPINION

International application No. PCT/CA98/00046

I. Basis of the opinion

1. This opinion has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed".*):

Description, pages:

1-35 as originally filed

Claims, No.:

1-52 as originally filed

Drawings, sheets:

1/19-19/19 as originally filed

2. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

3. This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1,2,5-18,21-48,52,

because:

- ☒ the said international application, or the said claims Nos. 35-37,43-52 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

- ☒ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. 1,2,5-18,21-48,52 are so unclear that no meaningful opinion could be formed (*specify*):

see separate sheet

- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|--------|-----------------|
| Novelty (N) | Claims | 3,19,20,49-51 |
| Inventive step (IS) | Claims | 3,4,19,20,49-51 |
| Industrial applicability (IA) | Claims | |

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

POINT III:

1. Claims 37 to 39, 43 o 52 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. Certain claims concerned "per se" compound which is defined by its ingredients or elements. Insofar that one ingredient is not defined, the compound could not be identified : see for instance in claim 1, wherein an element being defined as being an element having an ionic radius of 0.1 to 1.1A, which however did not give the definition of the concerned element. The same apply to claims 2,5-18,21 to 48,52. ✓

Further the "additive" is not defined in claim 16 nor in claim 17 and 52. ✓

POINT V:

1. Novelty:

J. of the Australian Ceramic Society, vol.29, n°1/02, 1993, pp.71-80 (2) - see page 71 paragraph 1 to page 72 paragraph 5, describes the biomaterial, subject - matter of claims 3, thus this claim seem to lack novelty.

WO - A - 91/17965 (3) - see abstract, page 5 paragraph 1 to paragraph 3, claims 1,6-10, describes the biomaterial compound, wherein the substitution element is silicon, thus claims 3,19,20,49-51 seem to lack novelty.

Solid State Ionics, vol.95, n°1/02, 1995,pp.121-129 (4) - see abstract, describes natural silicate - containing apatites.

US - A - 4 503 157 (5) - see abstract, column 4 line 66 to column 5 line17, column 10 example 2 , describes biocompatible apatite - mineral fibre composite.

WO - A - 95/32008 (6) - see abstract, page 11 lines 1-15, page 23 lines 7 to 22, page 30 lines 21-28, describes biomaterial implants based on hydroxyapatite.

FR - A - 2 664 501 (7) - see abstract, page 2 line 22 to page 3 line 8, claims 1,4,5 and 10, describes implant material based on phosphate calcium and collagen composite.

2. Inventive step:

It seem obvious for a skilled person to use a boron substitute in the biomaterial of the present application, further this material does not seem to bring advantages over the materials cited in the state of the art. The closest document seems to be (3) which brings biomaterial subject - matter of the present application, thus claims 3,4,19,20, 49 to 51 seem to lack inventive step.

3. Therapeutical treatment:

For the assessment of the present claims 35-37,43-52 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

POINT VIII:

Claims 7 and 15 specify that "calcium phosphate material" could be a " calcium oxide", which is impossible, thus these claims are not clear.

Further the last sentence in page 7 lines 28 to 30, is speculative and therefore it should be deleted.

PCT

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

| | | |
|--|-----------|---|
| (51) International Patent Classification ⁶ : A61L 27/00, C01B 33/24, 35/08 | A1 | (11) International Publication Number: WO 99/38542 (43) International Publication Date: 5 August 1999 (05.08.99) |
| (21) International Application Number: PCT/CA98/00046 (22) International Filing Date: 29 January 1998 (29.01.98) (71) Applicant (for all designated States except US): MILLENIUM BIOLOGIX, INC. [CA/CA]; Suite 200, 785 Midpark Drive, Kingston, Ontario K7M 7G3 (CA). (72) Inventors; and (75) Inventors/Applicants (for US only): PUGH, Sydney, M. [CA/CA]; 499 Maple Lawn Drive, Glenburnie, Ontario K0H 1S0 (CA). SMITH, Timothy, J., N. [CA/CA]; 21 Pickwick Place, Kingston, Ontario K7M 1M1 (CA). SAYER, Michael [CA/CA]; 97 Yonge Street, Kingston, Ontario K7M 1E4 (CA). LANGSTAFF, Sarah, Dorteia [CA/CA]; 35 Nelson Street, Kingston, Ontario K7L 3W6 (CA). (74) Agent: BARTOSZEWICZ, Lola, A.; Sim & McBurney, 6th floor, 330 University Avenue, Toronto, Ontario M5G 1R7 (CA). | | (81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> |
| (54) Title: A SYNTHETIC BIOMATERIAL COMPOUND | | |
| (57) Abstract The present invention is directed to a synthetic biomaterial compound based on stabilized calcium phosphates and more particularly to the molecular, structural and physical characterization of this compound. The compound comprises calcium, oxygen and phosphorous, wherein at least one of the elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1Å. The knowledge of the specific molecular and chemical properties of the compound allows for the development of several uses of the compound in various bone-related clinical conditions. | | |

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A Synthetic Biomaterial Compound

5 Field of the Invention

The present invention is directed to a synthetic biomaterial compound based on stabilized calcium phosphates and more particularly to the molecular, structural and physical characterization of this compound, herein called Skelite™.

10 Background of the Invention

It has long been the goal of biomaterials research in the field of orthopedics to develop synthetic structures exhibiting comprehensive bioactivity. Bioactive synthetic substrates capable of incorporation into the natural process of bone remodeling are of interest in applications which include *in vitro* bone cell assays [1], *in vivo* resorbable
15 bone cements [2, 3], implantable coatings which enhance the bonding of natural bone to the implant [4], various forms of implantable prostheses and bone repair agents [5, 6], and *ex vivo* tissue engineering [7]. The prime objective for such materials *in vivo* is to combine the stimulation of osteogenic activity in associated bone tissues for optimum healing, with the capability to be progressively resorbed by osteoclasts during normal
20 continuous remodeling [8]. *In vitro*, related functions are to provide standardized laboratory test substrates on which osteoclast resorptive function or osteoblast production of mineralized bone matrix can be assessed and quantified [1]. Such substrates must be stable and insoluble in the biological environment until acted upon by osteoclasts, the specific bone mineral resorbing cells.

25 While calcium hydroxyapatite ($\text{Ca}_5(\text{OH})(\text{PO}_4)_3$ or HA) is the primary inorganic component of natural bone [9], trace elements are also present [10]. Calcium hydroxyapatite is but one of a number of calcium-phosphorous (Ca-P) compounds which are biocompatible. Others include octacalcium phosphate [11] and both phases of tricalcium phosphate ($\text{Ca}_3(\text{PO}_4)_2$ or α -TCP / β -TCP) [12]. Compounds, particularly HA,
30 may show differing degrees of stoichiometry with the Ca/P ratio ranging from 1.55 to 2.2 [13]. Such materials can be artificially created by conventional high temperature ceramic processing [14] or by low temperature aqueous chemistry [15, 16]. Most of such artificial materials show good biocompatibility in that bone cells tolerate their presence with few deleterious effects, and indeed enhanced bone deposition may occur
35 [17, 18]. Currently, the most recognized medical application of calcium phosphates is the coating of implantable prosthetic devices and components by thermal or plasma spray to render the surface osteoconductive. It has been noted that Ca-P ceramics which

are stable in biological environments are often a mixture of individual compounds [19]. However, despite the osteogenic potential of these artificial materials, none actively participate in the full process of natural bone remodeling.

5 In the applicant's published international PCT application WO94/26972, cell-mediated resorption was shown to occur on a calcium phosphate-based thin film formed by the high temperature processing of a calcium phosphate colloidal suspension on quartz substrates. When used *in vitro*, these ceramic films exhibited multiple discrete resorption events (lacunae) across their surface as a result of osteoclast activity, with no evidence of dissolution arising from the culture medium. The regular margins of these
10 lacunae correspond closely to the size and shape of the ruffled borders normally produced by osteoclasts as the means by which they maintain the localized low pH required to naturally resorb bone mineral *in vivo*. Enhanced deposition of mineralized bone matrix also occurs on these ceramics in the presence of osteoblasts.

It was later revealed in the Applicant's published international PCT application
15 WO 97/09286, that these thin film ceramics exhibited two general characteristics: (1) the presence of a mixture of Ca-P containing phases comprising approximately 33% HA and approximately 67% of a silicon stabilized calcium phosphate and (2) a unique morphology. Importantly, it was noted that the thermal processing of the Ca-P colloid at 1000°C resulted in an HA powder, while the same colloidal suspension processed on
20 quartz had a mixed HA and silicon stabilized calcium phosphate phase composition. Energy dispersive X-ray analysis of the film demonstrated the presence of Si in the coating while cross-sectional transmission electron microscopy indicated a microporous physical structure.

In view of the clinical importance of developing a synthetic bone graft that is
25 both osteogenic and can participate in the body's natural cell-based remodeling process, it was important to focus on the role of introduced additives such as silicon in the formation of a calcium phosphate-based biomaterial compound capable of being assimilated and remodeled into natural bone with the aid of the activity of osteoclasts and osteoblasts. Since the compound could only be characterized by the preparation
30 method, it was crucial to be able to chemically characterize the compound beyond its microporous physical structure. In particular, it was important to characterize the specific molecular and chemical structure of the stabilized compound in order to be able to understand why the new compound worked so well in biological conditions affecting the skeleton. The molecular and chemical characterization of the compound could also
35 provide for the development of further uses of the compound in the treatment of several different types of bone-related clinical conditions. In addition, this would also allow

further chemical alteration of the compound in order that it could be designed for use in specific *in vivo*, *in vitro* and *ex vivo* applications.

The Applicants previous published work in WO 94/26872 and WO/97/09286 had pointed to the transformation of HA into a stabilized α -TCP phase. Surprisingly, during the difficult course of explicit characterization of the compound from a molecular standpoint, it was found that the resultant stabilized compound was in fact an entirely new compound herein described and termed Skelite™.

Summary of the Invention

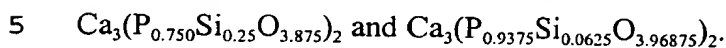
Stabilized calcium phosphate-based thin films and bulk ceramics have been created and have only now been specifically characterized with respect to their physical and chemical structure. The biomaterial compound is made by the high temperature processing of a fine precipitate, formed from a colloidal suspension and stabilized using an additive with an appropriate sized ionic radius that enables substitution into the Ca-P lattice. The compound typically coexists with calcium hydroxyapatite and is itself a novel stabilized calcium phosphate compound having a microporous morphology based on inter-connected particles of about 0.2-1.0 μ m in diameter. The compound is essentially insoluble in biological media but is resorbable when acted upon by osteoclasts. It also promotes organic bone matrix deposition by osteoblasts and can be assimilated into natural bone during the natural course of bone remodeling through the activity of osteoclasts and osteoblasts. The compound has been extensively analyzed using X-ray diffraction, infrared spectroscopy, nuclear magnetic resonance spectroscopy, and light scattering particle analysis. Results now indicate that the characteristic features of the compound arise during sintering through substitution reactions where a stabilizing element such as silicon enters the calcium phosphate lattice under conditions of high chemical reactivity. The crystallographic features are linked through the glaserite form of the apatite structure.

According to an aspect of the present invention a biomaterial compound is provided comprising calcium, oxygen and phosphorous, wherein at least one of the elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1Å.

According to another aspect of the present invention is a biomaterial compound having the formula $(Ca_{1-w}A_w)_i[(P_{1-x-y-z}B_xC_yD_z)O_j]_2$; wherein A is selected from those elements having an ionic radius of approximately 0.4 to 1.1Å; B, C and D are selected from those elements having an ionic radius of approximately 0.1 to 0.4Å; w is greater than or equal to zero but less than 1; x is greater than or equal to zero but less than 1; y is greater than or equal to zero but less than 1; z is greater than or equal

to zero but less than 1; $x + y + z$ is greater than zero but less than 1; i is greater than or equal to 2 but less than or equal to 4; and j equals $4 - \delta$, where δ is greater than or equal to zero but less than or equal to 1.

Specific compounds of the present invention include but are not limited to



The knowledge of the specific molecular and chemical properties of the compound of the present invention allows for the development of several uses of the compound in various bone-related clinical conditions. Such applications may include orthopedic, maxillo-facial and dental applications where the compound can be
10 fabricated to exist as a fine or coarse powder, pellets, three-dimensional shaped pieces, macroporous structures, thin films and coatings.

According to yet another aspect of the present invention is a method for substituting natural bone at sites of skeletal surgery in human and animal hosts with a biomaterial compound comprising calcium, oxygen and phosphorous wherein at least
15 one of the elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1 Å. The method comprises the steps of implanting the biomaterial compound at the site of skeletal surgery wherein such implantation promotes the formation of new bone tissue at the interfaces between the biomaterial compound and the host, the progressive removal of the biomaterial compound
20 primarily through osteoclast activity, and the replacement of that portion of the biomaterial compound removed by further formation of new bone tissue by osteoblast activity, such progressive removal and replacement being inherent in the natural bone remodeling process.

In accordance with another aspect of the present invention is a method for
25 repairing large segmental skeletal gaps and non-union fractures arising from trauma or surgery in human and animal hosts using a biomaterial compound comprising calcium, oxygen and phosphorous wherein at least one of the elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1 Å. The method comprises the steps of implanting the biomaterial compound at the site of the
30 segmental skeletal gap or non-union fracture wherein such implantation promotes the formation of new bone tissue at the interfaces between the biomaterial compound and the host, the progressive removal of the biomaterial compound primarily through osteoclast activity, and the replacement of that portion of the biomaterial compound removed by further formation of new bone tissue by osteoblast activity, such
35 progressive removal and replacement being inherent in the natural bone remodeling process.

According to yet another aspect of the present invention is a method for aiding

the attachment of implantable prostheses to skeletal sites and for maintaining the long term stability of the prostheses in human and animal hosts using a biomaterial compound comprising calcium, oxygen and phosphorous wherein at least one of the elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1Å. The method comprises the steps of coating selected regions of an implantable prosthesis with the biomaterial compound, implanting the coated prosthesis into a skeletal site wherein such implantation promotes the formation of new bone tissue at the interfaces between the biomaterial compound and the host, the generation of a secure interfacial bond between the host bone and the coating, the subsequent progressive removal of the coating primarily through osteoclast activity such that the coating is diminished, and the replacement of that portion of the biomaterial compound removed by further formation of new bone tissue to generate a secure interfacial bond directly between the host bone and the prosthesis.

According to yet another aspect of the present invention is a method for providing tissue-engineering scaffolds for bone replacement in human or animal hosts using a biomaterial compound comprising calcium, oxygen and phosphorous wherein at least one of the elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1Å. The method comprises the steps of forming the biomaterial compound as a macroporous structure comprising an open cell construction with interconnected voids, combining mature and/or precursor bone cells with the macroporous structure, and allowing the cells to infiltrate the structure in order to develop new mineralized matrix throughout the structure.

The knowledge of the structure of the novel compound of the present invention also allows for the use of the compound as a carrier for various pharmaceutical agents including but not restricted to bone growth factors and other agents affecting bone growth and remodeling.

According to another aspect of the present invention is a method for delivering pharmaceutical agents to the site of skeletal surgery in human or animal hosts using a biomaterial compound comprising calcium, oxygen and phosphorous wherein at least one of said elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1Å. The method comprises combining a pharmaceutical agent with the biomaterial compound and applying the pharmaceutical agent combined with the biomaterial compound to a site of skeletal surgery, wherein such application results in controlled local release of the pharmaceutical agent.

The biomaterial compound may be combined with additives such as those which increase the mechanical strength and toughness of the compound in order to provide additional functions for specific applications. The biomaterial compound

may also be combined with various calcium phosphate materials such as calcium hydroxyapatite, α -TCP, β -TCP, octocalcium phosphate, tetracalcium phosphate, dicalcium phosphate and calcium oxide either as a physical mixture or as a solid solution.

5 The biomaterial compound has a distinguishable microporous and nanoporous structure along with a crystallography that is similar yet different from that of α -TCP. The new compound exhibits monoclinic pseudo-rhombic symmetry and is in the monoclinic space group $P2_1/a$. Furthermore, the new compound has a portion of the phosphorous substituted by an element having a suitable ionic radius.

10 The knowledge of the chemical formula of the biomaterial compound and the mechanism behind its bioactivity and stability in biological environments allows for the use of this compound *in vivo* for the treatment of various bone related clinical conditions. In particular, the compound may be used to help repair and restore natural bone that has been compromised by disease, trauma, or genetic influences.

15

Brief Description of the Drawings

The present invention will be further understood from the following description with reference to the Figures, in which:

20 Figure 1 shows a X-Ray Diffraction Spectrum (θ - 2θ) of powder prepared from the Ca-P colloid with no introduced additives and sintered at 1000 ° C.

Figure 2 shows glancing angle XRD spectra of a thin film of the Ca-P colloid sintered on quartz at 1000 ° C.

Figure 3 shows GA-XRD spectra illustrating the effect of sintering temperature on thin film phase composition;

25 Figure 4 shows GA-XRD spectra illustrating the effect of sintering time on thin film phase composition;

Figure 5 shows a SEM micrograph illustrating the characteristic surface morphology of a thin film of the Ca-P colloid sintered on quartz at 1000 ° C;

30 Figure 6 is a cross-sectional TEM of a Ca-P thin film on quartz, (a) film sintered at 1000°C (b) unsintered film;

Figure 7 shows the average agglomerate size in the Ca-P colloid as a function of colloid aging period, as determined using light scattering particle analysis;

Figure 8 shows a calculated predominance area diagram illustrating the effect of CaO activity on the relative stabilities of HA and TCP;

35 Figure 9 shows a θ 2 θ XRD spectrum of powder prepared from the Ca-P colloid with silicon as the introduced additive. Approximate phase ratio: 33 \pm 5% HA and 67 \pm 5% Si-TCP;

Figure 10 shows the effect of silicon content on phase composition of Si- mHA powders, as determined by x-ray diffraction (θ -2 θ);

Figure 11 shows SEM micrographs illustrating the characteristic surface morphology of Si-mHA ceramic pellets. Si-mHA pellets can be resorbed by the specific cellular activity of osteoclasts in a manner similar to that which occurs on natural bone. (a) Surface morphology Si-mHA ceramic pellet; (b) Osteoclast lacunae on surface of Si-mHA ceramic pellet; and 11(c) Osteoclast lacunae on surface of natural bone;

Figure 12 shows θ -2 θ XRD spectra of powder prepared from the Ca-P colloid with titanium as the introduced additive.

Figure 13 shows the effect of Ti addition on mHA phase composition; (a) no carrier (powder), (b) no carrier (ceramic pellet), (c) 2Me (powder), (d) 2Me (ceramic pellet), (e) ACAC (powder) and (f) ACAC (ceramic pellet);

Figure 14 shows SEM micrographs comparing the microstructure of Si-mHA pellets formed from the Ca-P colloid versus materials prepared from commercial sources. (a) Si-mHA prepared using TPOS as the introduced additive; and (b) cHA as a physical mixture with TPOS.

Figure 15 shows the XRD spectra for the physical mixture of 25% CaSiO_3 and 75% β -TCP sintered at 1250°C for 8 hours;

Figure 16 shows a high resolution XRD spectrum of Si-mHA powder;

Figure 17 shows the NMR spectra comparing Si-mHA with commercially available reference materials; (a) mixture of commercial CaSiO_3 and SiO_2 powders, (b) Si-mHA powder;

Figure 18 shows IR spectra for powders sintered at 1000 °C: (a) cHA, (b) mHA and (c) Si-mHA; and

Figure 19 shows a summary of the IR spectra illustrating the effect of silicon content on the P-O stretch.

In the drawings, preferred embodiments of the invention are illustrated by way of example. It is to be expressly understood that the description and drawings are only for the purpose of illustration and as an aid to understanding, and are not intended as a definition of the limits of the invention.

Detailed Description of the Preferred Embodiments

The Applicants have developed a process to provide a stabilized calcium phosphate synthetic biomaterial compound which is fully biocompatible and has a surface morphology capable of consistently supporting bone cell activity thereon. This is provided in accordance with that method described in the Applicant's co-pending published PCT application WO 97/09286, the subject matter of which is incorporated herein by reference. The preferred embodiment for making the compound of the present invention is described herein in the accompanying examples.

The compound of the present invention is herein referred to as a biomaterial compound due to its bioactive nature in both *in vitro* and *in vivo* systems. Bioactivity refers to the ability of the biomaterial compound to support osteoclast and osteoblast activity and the ability to be assimilated with natural bone by the activity of these cells. Although the compound was characterized with respect to the process by which it is made as well by its surface morphology, the molecular structure was unknown and could not be determined. It was however essential to characterize the compound further with respect to its chemical structure so as to better understand the properties of the compound as well as to understand why the compound was so well adapted for osteoclast and osteoblast activity. The knowledge of the chemical structure of the compound also allows for the modification of the compound for therapeutic use in the treatment of certain clinical conditions.

It was initially thought as described in WO 97/09286 that the compound was a silicon stabilized α -TCP. However, with further difficult and tedious analysis it was surprisingly found that the compound was in fact a completely new compound never before characterized and herein referred to as Skelite™. Where silicon is used as the introduced additive to form Skelite™ the compound is referred to as Si-TCP. One reason for the great difficulty in establishing the chemical formula for the new compound was due to the complex and large structure of Ca-P compounds such as HA as well as the changing phase transitions that occurred during the sintering process. The chemical identification of this compound was only realized and developed after lengthy analysis of various Ca-P powders, thin films and pellets prepared with introduced additives in accordance with that described in WO 94/26872 and WO 97/09286. Consistent with that disclosed in applicant's international application WO 97/09286, standard XRD analysis was performed on samples prepared by a variety of compositional and thermal processing routes. Results were initially considered to be consistent with the conclusion that the materials were a mixture of α -TCP and HA, and that the calcium silicates predicted by the FACT database [23] existed as a glassy phase at the grain boundaries. Since no JCPDS file was available for Skelite™ and the peak

positions were indicative of α -TCP using standard XRD techniques, the identification of Skelite™ was unforeseen. Furthermore, one would not expect to find that substitution is taking place at such low temperatures. A complex and unobvious combination of analysis techniques had to be performed to successfully identify and characterize the new compound. These studies, described as follows led to the characterization of the new compound, an additive stabilized calcium phosphate compound, Skelite™.

For clarity, several materials referred to herein are defined as follows. For the commercially available materials cHA refers to commercial calcium hydroxyapatite (HA), calcium silicate refers to CaSiO_3 and silica refers to SiO_2 . For the internally prepared materials mHA refers to microporous calcium hydroxyapatite (HA), Si-mHA refers to Si-TCP plus mHA. These materials are further defined in Table 1.

Analysis of Pure (No Introduced Additives) mHA Powders

Using reaction (1) and analogous reactions, a fine colloidal precipitate of HA in ammoniated water can be achieved under conditions where the pH is greater than 10.

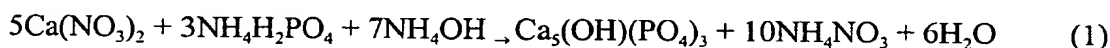


Figure 1 shows that powders prepared from the colloidal suspension of equation (1) with no introduced additives and sintered at 1000°C are HA (JCPDS File #9-432). The particle size of sintered powders, after mild grinding following sintering, is about $1\ \mu\text{m}$ as determined by SEM.

Analysis of Thin Films on Quartz Substrates

Figure 2 shows that the film on quartz has a crystallographic structure which was more complex than that for a powder sintered under the same conditions. The structure consists of two major phases, HA and Si-TCP, where the Si-TCP resembles, but is different from the crystallography of α -TCP (JCPDS file #9-348). All peaks within the XRD spectra could be attributed to either HA or Si-TCP and no distributions of peaks characteristic of other phases (such as β -TCP or octacalcium phosphate) were distinguishable from background.

Figure 3 shows that as the sintering temperature was increased, the film composition changed. When the film was fired for one hour at 800°C the composition of the film was 94% HA and 6% Si-TCP; at 900°C there was a mixture of 62% HA and 38% Si-TCP; at 1000°C the composition was 33% HA and 67% Si-TCP. Changes in composition and film morphology as a function of sintering duration were assessed by changing the time the thin film on quartz remained in a furnace maintained at a set

temperature. A computer controlled system allowed the ramp rate and hold temperature to be defined. Figure 4 shows that a dwell time of five minutes yielded the same equilibrium phase composition as observed after a one hour dwell time. Increased dwell time resulted in grain growth, as shown by SEM studies.

5 The phase composition could be modified by changing the humidity of the sintering environment while maintaining the firing conditions at 1000°C for one hour. The reaction was suppressed by the presence of increased water vapor. Other external factors or the addition of additives to the colloid suspension did not significantly modify the results achieved for thin films on quartz.

10 Optical microscopy, SEM and TEM show that the sintered films on quartz have a consistent morphology which is illustrated in Figures 5 and 6(a). While the films appear to be composed of translucent polycrystals under an optical microscope with phase contrast (x20), at the higher magnification achieved using an SEM (x10K) the surface morphology is that of an interconnected set of rounded particles with a high
15 degree of porosity as seen in Figure 5. The average dimension of these particles depends on the time and temperature of sintering. Under most conditions the mean size lies between 0.2 and 1 μm with the size increasing with the time and temperature of sintering. Cross-sectional TEM (Figure 6(a)) of an individual particle indicates the presence of nanoporosity within the body of the particle. It is important to note that
20 these pores were not altered with extended exposure to the electron beam, and were therefore inherent to the sample and not a sample preparation artifact. The underlying granular structure was about 5-10 nm in size. This appeared to reflect the individual granule size observed in the cross-sectional TEM micrographs of a dried but unsintered thin film on quartz as seen in Figure 6(b).

25 To examine the evolution of particle agglomeration, aliquots of the colloidal suspension were analyzed for particle size after various aging times. Figure 7 shows that a marked variation in measured particle size occurs during the 24 hour period of aging. The initial measurement gives a particle size less than 1 μm , increasing to greater than 10 μm after 8 hours, but subsequently decreasing again to approximately 1 μm
30 after 24 hours. This is indicative of agglomeration of the fine precipitate with the most stable structure having dimensions in the range of 0.2-1.0 μm . Subsequent sintering of such agglomerates accounts both for the basic morphology of the thin films on quartz and the microporosity of bulk ceramics

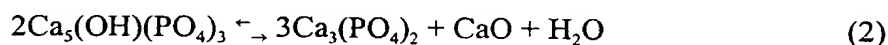
35 In order to understand the origin of the difference between a precipitate fired as a powder or as a thin film prepared on a quartz substrate, films on quartz were fired for 1 hour and were subsequently analyzed for elemental composition as a function of distance from the quartz interface using electron induced energy dispersive X-ray

spectroscopy (EDX). Silicon was detected at concentrations which decreased with distance from the interface; however, no XRD peaks for compounds such as calcium silicate could be identified. These results suggested that Si diffusing from the quartz substrate played a role in modifying the morphology and crystallography of the thin films.

Analysis of mHA Powders with Introduced Additives

Powders prepared from the colloid of equation (1) combined with selective additives, demonstrate a unique calcium phosphate composition after sintering at 1000°C. Several possible actions of silicon as an additive in this temperature range were initially postulated such as the modification of the conversion reactions of HA into its successor compounds; the modification of the crystallographic structure of HA and its successor products by silicon substitution; and morphological changes associated with surface diffusion of the additive or by additive induced changes in surface properties.

These possibilities were evaluated by the creation of ceramic thin films, powders and bulk materials in which processing conditions or the presence of additives changed the final products. The initial basis for defining process changes and additive selection was determined according to equilibrium thermodynamic computations using the database and programming in the Facility for the Analysis of Chemical Thermodynamics (FACT)[23]. Figure 8 shows the calculated phase diagram expected for the Ca-P system as a function of inverse temperature (K^{-1}) and partial pressure of H_2O in the thermal processing atmosphere. The diagram applies to a closed chemical system and utilizes a large database of literature values for the Gibbs free energies of formation. The most stable phase(s) are computed for a large matrix of coordinates which lead to the placement of the phase boundaries. HA decomposes into β -TCP at temperatures below 1100°C under low partial pressure of H_2O . α -TCP is formed at temperatures above about 1100°C. The predictions are consistent with high temperature crystallographic data for HA ceramics [24, 25]. The decomposition reaction, corresponding to the lowest diagonal line on the diagram, may be written as equation (2):



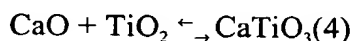
Since the conversion of HA into TCP results in the simultaneous formation of CaO and release of H_2O , changes in the activity of both CaO and H_2O should modify the location of the phase boundaries. The upper diagonal lines show the phase boundary when the activity of CaO is made progressively smaller. This effect can be practically

accomplished by chemical combination of CaO with other compounds such as SiO₂. In the presence of silica (SiO₂), the resultant compound could be one or more of several calcium silicates. The calculations show that the decomposition boundaries in the temperature range of 800-1100°C are in approximate agreement if CaO has the activity
5 expected when the CaO is combined with SiO₂ as follows in equation (3):



The most stable phosphorous-containing conversion product is, however, β-TCP. This is consistent with the widespread observation of the magnesium doped HA-based mineral whitlockite as the natural form of β-Ca₃(PO₄)₂ [25]. On the basis of the information available within the FACT database it is not possible to explain the
10 observation of a phase similar to α-TCP as a conversion product below 1000°C other than to assume that β-TCP is not nucleated when CaSiO₃ forms and that Si-TCP develops as a metastable allotropic form.

It may be noted that on the basis of chemical thermodynamics, any reaction which changes the activity of CaO should modify the phase diagram. Oxides such as
15 TiO₂ have only one product with CaO as in equation (4):



and may therefore be more predictable in their action. Similar calculations to those for Si showed that for a similar partial pressure of water, the phase boundary for Ti was located at a slightly lower temperature.

Figure 9 shows that the XRD pattern for a powder prepared using an additive
20 concentration of 1 mol SiO₂ to 1 mol mHA is similar to that obtained for thin films on quartz. For this sample, the silicon was added as tetrapropyl orthosilicate in 2-methoxyethanol. The spectrum was compared to JCPDS files and concluded to be a mixture of HA and Si-TCP. Subsequent experiments demonstrated that the phase composition was independent of whether the additive was introduced with 2-
25 methoxymethanol, 2-4 pentanedione or no carrier. Figure 10 shows the phase composition of powders sintered at 1000°C for one hour as a function of silicon content, as determined by XRD. The phases present switch from predominantly HA to predominantly a new compound (Si-TCP) at a relative molar Si/mHA ratio of approximately 0.6. The conversion is slightly greater when powders are formed into
30 ceramic pellets. While the specific level of conversion is dependent on processing conditions, the typical Si-TCP:HA range is 20:80 to 80:20. Due to the increased signal to noise ratio and a more linear change of the background as a function of 2θ evident in the θ-2θ XRD spectra of the powders, the accuracy of determination of the phase

composition in powders is increased. Additive saturation is evident at molar ratios exceeding 1:1 indicating process constraints in the integration of further silicon. Figure 11(a) shows that the crystalline morphology of a pellet formed from Si-mHA was similar to that observed in the thin films on quartz. The ceramic comprises rounded, inter-connected particles of average size 0.2 - 1.0 μm with a large degree of localized porosity. Varying the compound preparation condition permits the formation of a range of microporous structures comprised of particles of size range 0.1 to 2.0 μm . Figure 11(b) indicates that Si-mHA materials show strong evidence of osteoclastic resorption similar to that which occurs on natural bone as shown in Figure 11(c).

The XRD pattern for powders prepared using Ti as the additive also showed that conversion occurs upon addition of the Ti. However, the results were more complex as the predominant phase of TCP formed was β -TCP (Figure 12) with the degree of conversion dependent on the carrier used with the additive. Furthermore, there was enhancement of the degree of conversion on powder grinding and processing to form ceramic pellets. The results are summarized in Figure 13. Figures 13(a) and 13(b) respectively show the effects of titanium addition with no carrier for powders and ceramic pellets. Substantial conversion only occurs for pellets which were formed by grinding, pressing and resintering the original powder. The addition of titanium is similar or even less effective when 2Me is used as the carrier (Figures 13(c) and 13(d)). Substantial conversion at approximately 0.5 mol TiO_2 per mol mHA occurs in powders only when ACAC is used as a carrier and again this conversion occurs more effectively in the reground pellets, Figures 13(e) and 13(f). Particularly in the ceramic pellets, the phase composition shows a substantial fraction of β -TCP. The microstructure of pellets created from powders where Ti was the additive showed a particle size of approximately 0.3 μm .

The simplest interpretation of the differences between the effects of Si and Ti additives is based on the observation of the effects of additive precipitation and the changes observed in degree of conversion following powder grinding and pellet formation. In the case of Si-based additions, the degree of precipitation was essentially independent of the carrier and relatively minor changes in the degree of conversion occurred on formation into ceramic pellets. In contrast, Ti additions were ineffective when precipitation occurred when the additive was introduced into the Ca-P colloidal suspension (for no carrier and 2Me). Ti additions were effective when precipitation did not occur (for ACAC) and conversion became stronger upon grinding of the powder to form pellets and subsequent resintering. This suggests that the conversion from HA to TCP requires intimate contact between the additive and HA, possibly through surface functionalization of the precipitated mHA particles within the colloid suspension by the

additive species or adsorption of the additive species on the surface of the mHA particle. When the additive and the mHA precipitate as separate species, the conversion occurs only upon strong physical inter-mixing and thermal treatment.

For comparative purposes, reference materials were prepared by equivalent thermal processing of commercially available powders (see Table 1) in an attempt to produce ceramics with a similar phase composition and surface morphology. Commercial powders were processed as pure compounds and in combination with selective additives introduced either as inorganic powders or as metallorganic species in a carrier. XRD results indicate that conversion of commercial HA (cHA) does take place, but that the primary resultant phase is β -TCP. The typical phase distribution is 73% β -TCP, 20% α -TCP and 7% HA. These results are consistent with the phase composition predicted by thermodynamics as noted in equations (2) and (3) and illustrated in Figure 8. Of equal significance is that the surface morphology of the ceramics prepared from these powders exhibits a jagged or fractured morphology (Figure 14b) with little inter-connectedness, and a particle size an order of magnitude greater than observed in colloid-based mHA pellets (Figure 14a). Evidence for a microporous morphology is restricted to the surface region of the particles. Pellets prepared in this fashion show no indication of resorption by osteoclasts.

The solid state chemistry of the cHA powders with introduced additives suggest that the conversion behaviour as a function of temperature, humidity and additive is consistent with equations (2)-(4). In particular, if physical mixing of the additive into the cHA powders takes place the β -TCP phase predicted by chemical thermodynamics is observed. In comparison, if intimate mixing of an unprecipitated silicon additive and a Ca-P colloid occurs the resultant phase is Si-TCP. This phase is not consistent with the predictions of equilibrium thermodynamics, but it is closely linked with the presence of Si in the Ca-P lattice. In order to use the FACT database to predict the phase boundaries for transitions to this SkeliteTM compound, new values for the Gibbs free energy will be required.

The origin of the SkeliteTM compound and confirmation of the mechanism of formation was investigated using techniques which assess the location of the additive within the HA or TCP structures, in an attempt to observe the presence of the reaction products predicted by equations (3) and (4).

Significantly, no calcium silicate peaks were identifiable in XRD spectra taken on either colloidal-based or mixed powder compositions where Si was the selected additive. This suggests that Si forms a dispersed or substituted phase within the phosphate lattice. Previous workers [26, 27] have suggested that calcium silicate and β -TCP form a miscible solid solution at high temperatures ($>1350^{\circ}\text{C}$) over the

composition range of interest. The XRD spectra reported in these earlier experiments did not match that of α -TCP or the Skelite™ presently described, thus demonstrating the uniqueness of this compound. In this work, when commercially available CaSiO_3 was physically mixed with cHA or β -TCP powders (Table 1) and then sintered for 8 hr in alumina crucibles in air at 1250°C , the results showed that CaSiO_3 nucleates a crystallographic phase consistent with the Skelite™ compound (Si-TCP) (Figure 15). The degree of conversion to Skelite™ increases as the temperature of the reaction is increased. At 1250°C and above, depending on the amount of Si present, the powder mixtures show an increasing tendency to form a melt thus eliminating the microporous structure.

Comparison of three major peaks in the XRD spectrum of Skelite™ and α -TCP between $2\theta_{\text{Cu}}=30$ and $2\theta_{\text{Cu}}=31^\circ$, assuming a Gaussian theoretical peak shape with a width of 0.225° , shows that there is a shift of approximately 0.1° to lower 2θ in Si-TCP (Figure 16) resulting from an increase in the lattice parameters. The presence of this significant shift was confirmed through the close examination of the position of the HA peak present in the XRD spectra. The HA peak, $2\theta_{\text{Cu}}=31.8^\circ$, was within 0.01° of that predicted by the JCPDS file, and hence the accurate calibration of the instrument was assured. A peak shift in the α -TCP XRD spectra to lower 2θ would occur if Si^{4+} ($\text{IR}=0.26 \text{ \AA}$ for $\text{CN}=4$) substitutes at P^{5+} ($\text{IR}=0.17 \text{ \AA}$ for $\text{CN}=4$) sites, although the effect would not be large since the lattice structure is dominated by the oxygen polyhedra of the TCP. The fact that the substitution reaction occurs at 1000°C only for colloidal particles in which the Si is chemically functionalized on the surface suggests that the substitution kinetics are very slow in the low temperature range.

Nuclear Magnetic Resonance Studies

Magic-angle NMR studies were carried out on Si-mHA powders. Comparisons were made with simple physical mixtures of cHA, α - and β -TCP, CaSiO_3 and SiO_2 in proportions similar to the phases present in the Si-mHA powders. For Si-mHA, no Si signals could be observed under any conditions of measurement. Careful comparison with signals measured on CaSiO_3 and amorphous SiO_2 was used to set the lowest level of sensitivity at which the compounds or local structures could be measured. Figure 17 compares NMR spectra, signal averaged over 120,000 pulses, for Si-mHA with that obtained from a simple physical mixture of cHA and 10% of equal parts of CaSiO_3 and SiO_2 . The absence of any NMR signal in the Si-mHA indicates that Si is highly dispersed throughout the crystallographic structure of mHA so that no clearly definable location or compound could be identified.

Infrared Spectroscopy Studies

Figure 18 compares infrared spectra for sintered powders of (a) cHA, (b) mHA, and (c) Si-mHA. The peak pair found at the lowest wavenumbers near 600 cm^{-1} indicate the presence of similar but not identical bonds. The spectra for cHA and mHA powders (no additives) were otherwise generally similar. Silicon addition causes a substantial narrowing of the P-O stretch peak and a shift in its position from 1048 to 1065 cm^{-1} (Figure 19).

In order to assess these changes, IR spectra of CaSiO_3 , CaO, SiO_2 and commercial β -TCP were examined. The CaSiO_3 spectrum shows a series of distinctive peaks at 717, 563 and 434 cm^{-1} that are not apparent anywhere in the spectra for Si-mHA powders. The CaO spectrum has a strong sequence of bands below 463 cm^{-1} which are also not observed in the Si-mHA spectrum. The SiO_2 spectrum shows a very strong, well-resolved peak at 1104 cm^{-1} characteristic of the Si-O bond. An interpretation of the Si-mHA spectra is that the Si-O bond absorption occurs at lower wave numbers than in the pure SiO_2 . The apparent shift in the P-O stretch can be explained by the growth of a Si-O peak. It is logical that the Si-O and P-O peaks would occur at similar positions since silicon and phosphorus are located beside each other in the periodic table and have similar ionic radii. The fact that the P-O peak appears to shift further indicates the formation of a new silicon compound, Skelite™.

A structural model for silicon substitution based on the IR analysis is a crystal lattice of TCP-like and HA-like material with molecular dispersion of silicon throughout the lattice. This is consistent with the NMR and XRD results. The narrowing of the P-O peak suggests the existence of a less broad distribution of types of P-O bonds within the structure or an increase in crystallinity compared to the mHA with no introduced additives.

The Skelite™ Compound

The significant correlations with cell-based bioactivity and resistance to dissolution at normal physiological pH 6.4 to 7.3 are the presence of the additive stabilized compound and the microporous morphology. The morphology is accounted for by the sintering of particles of average size 0.2 to 1.0 μm . The presence of a Si-TCP phase that is essentially insoluble in biological media at low temperature using silicon as the introduced additive is unexpected and is induced by the distribution of Si substituted throughout the structure. Considering that the underlying structure of the particles is the agglomeration of granules of size range of approximately 1 to 20 nm, uniform

dispersion of the silicon additive and functionalization of the surface of an individual granule is assured by permeation of the silicon sol throughout the agglomerate. The key aspect of this investigation was the determination that silicon does not induce an α -TCP phase resulting from the decomposition of HA, but rather it creates a Si-TCP phase, a new biomaterial compound, by substitution of silicon at phosphorus sites. The fact that silicon induces a Si-TCP compound can now be explained through the crystallography of the calcium-phosphate system and the defect chemistry associated with silicon substitution into the Ca-P lattice. One skilled in the art would understand that other additives having an ionic radius which is different to that of silicon as described herein, but may still substitute into the Ca-P lattice is also embodied for the compound of the present invention. Therefore the compound is not restricted only to silicon as the additive.

It is important to note that "effective ionic radius" has been selected as the term of reference in these studies [34]. The ionic radius specifications provided herein reflect the effective ionic radius for coordination numbers of 4, 6 or 8. It is apparent to those skilled in the art that "ionic crystal radius" may also be used in the practice of the present invention and thus may be used to define equivalent specifications for the compound and the formula of the compound as described herein. A summary of the effective ionic radius and the ionic crystal radius for various elements is provided in Table 2.

When substituting Si in the HA lattice, the ionic radius of Si^{4+} ($\text{IR}=0.26\text{\AA}$ for $\text{CN}=4$) suggests that Si^{4+} can enter at P^{5+} ($\text{IR}=0.17\text{\AA}$ for $\text{CN}=4$) sites within the PO_4^{3-} tetrahedra although it could also be included at Ca^{2+} ($\text{IR}=1.0\text{\AA}$ for $\text{CN}=6$) sites. The lattice strain and compensating defect will be significantly different in the two cases and the effects of covalency will substantially modify the result. A low temperature substitution of Si^{4+} into P^{5+} sites creates less strain and accommodates the covalency well. The radius ratio for silicon and oxygen is consistent with that required for the tetrahedral coordination of silicon in an oxygen lattice. Such a substitution requires the formation of a single positively charged defect for charge compensation. An obvious defect is one oxygen vacancy for every two silicon ions, although the energy required to displace oxygen-phosphorous bonds within an already formed PO_4^{3-} tetrahedron may be substantial. Theoretically, substitution of an ion with an appropriate ionic radius and a valence of ≥ 3 at Ca^{2+} sites could also provide charge compensation. Such elements may include Ce, La, Sc, Y and Zr. Restrictions on the use of particular elements may be present due to the particular applications for use as a biomaterial.

In the formation of the Si-TCP compound, compositional analysis suggests that the Ca:P ratio decreases from approximately 1.67 (HA) to 1.5 (TCP). This could be

induced by (1) the removal of calcium from the lattice, or (2) the introduction of additional phosphorous or an element that substitutes for phosphorous. A reduction in the calcium content of the lattice could theoretically occur by the formation of calcium silicate distributed within the structure. However, no evidence of calcium silicates as a well defined compound can be found in either the NMR or the IR results. Thus extensive silicon substitution must occur forming a multitude of Si-substituted P-O sites in the lattice.

In the case of Ti^{4+} , the ionic radius of ($r_{\text{Ti}}=0.42\text{\AA}$ for CN=4) likely precludes its substitution at P^{5+} sites and it must therefore enter the crystal at more general interstitial sites within the lattice. Since titanium has been demonstrated to be less effective in modifying the crystal structure to create a stabilized TCP, this suggests that the nucleation of the Si-TCP phase is intimately connected with the substitution of silicon at phosphorous sites. In particular, the observed phase being in fact a Ca-P-Si compound with a crystallographic structure similar but different from α -TCP rather than pure α -TCP, resolves conflicts with respect to the new compound's decreased solubility and the predicted decomposition phase diagram.

The crystallography of the Ca-P phase diagram has been extensively studied and compared [12] in apatites [28], β -TCP [29, 30] and α -TCP [31]. Significant differences have been noted between the structures of α and β -TCP [12, 31] and equally significant similarities have been seen between α -TCP, apatites and calcium silico-phosphate compounds via the glaserite structure [32]. A primary component of the phosphate lattice is the presence of PO_4^{3-} tetrahedra, although these structures can vary considerably throughout a complex lattice. For example, in α -TCP the P-O distances vary from 1.516 to 1.568 \AA and the O-P-O angles vary from 104.1 to 115.2° [31]. Substitution of a Si at such sites implies a range of environments for such an additive.

Following Elliott [33] the space group of HA has three kinds of vertical or columnar symmetry. There are columns of Ca^{2+} ions spaced by one half of the c-axis parameter along three-fold axes which account for two-fifths of the Ca^{2+} ions in the structure. These ions are given the designation Ca(1). The Ca^{2+} ions are linked together by PO_4 tetrahedra in which three oxygen atoms come from one column and the fourth comes from an adjacent column. The result is a three-dimensional network of PO_4 tetrahedra with enmeshed Ca^{2+} ions, and channels that contain the residual calcium, Ca(2), and ions such as OH^- which make up the HA structure.

The α -TCP structure also comprises columns of Ca^{2+} and PO_4^{3-} ions parallel to the c-axis [28]. The columns are actually anion-anion columns ...Ca Ca Ca Ca.... and cation-anion columns ... PO_4 Ca PO_4 \square PO_4 Ca PO_4 \square PO_4 Ca PO_4 where \square is a vacancy [12]. The presence of this vacancy may facilitate the creation of O^{2-} vacancies

in neighboring PO_4^{3-} tetrahedra required to accommodate the substitution of Si^{4+} at P^{5+} sites. Analogous cation-anion columns occur in glaserite, $\text{K}_3\text{Na}(\text{SO}_4)_2$, except that the vacancy is occupied by a K^+ ion. Strong similarities exist between the glaserite and apatite structures [26]. The apatite structure can be derived from that of α -TCP by replacing cation-cation columns at the corner of the apatite unit cell by anion columns (OH^- or F^-). The remaining cation columns in α -TCP become the columnar $\text{Ca}(1)$ ions in apatite, whilst the PO_4^{3-} and Ca^{2+} ions that form the cation-anion columns in α -TCP have approximately the same positions as the PO_4^{3-} and $\text{Ca}(2)$ ions in apatite. Of significance to this analysis is that the glaserite structure is related to silico-carnotite $\text{Ca}_5(\text{PO}_4)_2\text{SiO}_4$ [30] and α - Ca_2SiO_4 [31]. This is consistent with the report that the system Ca_2SiO_4 - $\text{Ca}_3(\text{PO}_4)_2$ forms a continuous series of solid solutions at higher temperatures based on the glaserite structure [27].

In contrast, there are no such similarities between the structure of HA and β -TCP. The β -TCP structure is a distortion of the parent lattice, $\text{Ba}_3(\text{VO}_4)_2$, with layers perpendicular to the c-axis. There is no columnar relationship between cations in the structure. Because of the size of the Ca^{2+} ion, there is a reduction in the number of PO_4 tetrahedra in the structure compared to that for the parent lattice and a reduction in the number of formula units within the hexagonal unit cell. Two types of Ca sites exist within the β -TCP unit cell: those known as Ca(5) are fully occupied, while a particular set of cation sites known as Ca(4) are only half occupied [12]. Upon doping TCP with Mg^{2+} ($\text{IR}=0.72\text{\AA}$ for $\text{CN}=6$) the Mg distributes itself first randomly on the Ca(4) and Ca(5) sites, but subsequently only substitutes at the Ca(5) sites. Because Mg^{2+} is smaller than Ca^{2+} ($\text{IR}=1.0\text{\AA}$ for $\text{CN}=6$) and the original distortion of the $\text{Ba}_3(\text{VO}_4)_2$ structure occurred because Ca^{2+} is smaller than Ba^{2+} ($\text{IR}=1.35\text{\AA}$ for $\text{CN}=6$), the β -TCP structure is stabilized with the addition of Mg^{2+} to form the naturally occurring mineral, whitlockite [31]. Indeed the addition of Mg to β -TCP at high temperatures tends to stabilize the structure well into the α -TCP range. In the case of the addition of an ion such as Ti^{4+} , the slightly larger ionic radius ($\text{IR}=0.61\text{\AA}$ for $\text{CN}=6$) would suggest that it would also be accommodated by substitution at Ca(5) cation sites with results that are less defined than for Mg^{2+} . Since charge compensating defects are necessary, the stabilization or creation of Ca^{2+} vacancies on Ca(4) sites would serve this purpose. Therefore substitutional Ti should stabilize the β -phase once TCP has been formed.

A feature of the presently characterized compound is that the SkeliteTM structure is only achieved when intimate contact occurs between the precipitate and the additive. When silicon is introduced into already formed and fired powders at relatively low temperatures, the resulting post-sintered phase is predominantly β -TCP. In this case the

silicon plays a role similar to that described for titanium above and simply acts to reduce the activity of CaO in the decomposition of HA under the terms of equation (3). In the case of colloidal powders precipitated in close association with an additive such as silicon, both the surface activity will be high and strongly functionalized complexes will be formed in the solution and at the interfaces of the precipitated granules. Through sintering, a range of PO_4^{3-} and SiO_4^{4-} tetrahedra will be established along with the necessary oxygen vacancies. In this case, nucleation of the glaserite-based Si/P phase will take place. While previously this was interpreted as a form of α -TCP it is, in fact, an entirely different compound with its own values for solubility and bioactivity (Si-TCP). Thus the crystal phase composition, surface morphology and bulk morphology originates from the chemically active and agglomerated state in which the starting material is precipitated, and the degree to which this state controls the location at which the Si^{4+} cation is substituted.

Again, although silicon has been the most extensively studied and appears to be the preferred substituted element of the invention, it is apparent to one skilled in the art, that any additive that can enter and distribute throughout the crystal structure of the calcium phosphate lattice and result in the compound of the present invention can be substituted for silicon. Therefore, the present compound is not restricted to only silicon as the substituted element but may also include other suitable elements having a suitable ionic radius of approximately 0.1-0.4Å such as for example boron. It is also understood that other additives in addition to the silicon or boron may also be present in the compound of the present invention. Such elements may also form part of the Ca-P lattice where such elements and/or the amount of oxygen may act to balance charge compensation for additives incorporated into the compound. Such additives may be selected from the group consisting of Ce, La, Sc, Y, and Zr.

It is also understood by those skilled in the art that the novel compound of the present invention can be combined with a calcium phosphate material such as calcium hydroxyapatite, α -TCP, β -TCP, octocalcium phosphate, tetracalcium phosphate, dicalcium phosphate, calcium oxide and other like materials. The resultant combination can be as a physical mixture or as a solid solution. In addition, other additives such as polymers or microfibers may additionally be added to the compound of the present invention to increase mechanical strength and toughness. The particle size of these additives may be selected such that the additive may be removed through phagocytosis by the action of macrophages. Metals may also be present in combination with the present compound to form composite structures. Such structures are also intended to be embodied in the present invention

In summary, a new calcium phosphate-based biomaterial compound has been created and specifically characterized. This new biomaterial exhibits two prominent features:

- (1) A unique composition created by the introduction of additives, such as silicon, into the colloidal precipitate to form upon sintering a stabilized calcium phosphate phase comprising the novel compound.
- (2) A characteristic microporous morphology that arises from the agglomeration of particles within the colloid precipitate and the sintering of the material to produce a network of interconnected particles.

It is now revealed via numerous difficult analytical tests and complex data interpretation that this stabilized calcium phosphate compound is a novel additive stabilized structure referred to as Skelite™ that may exist in combination with HA, α -TCP, β -TCP or other suitable calcium phosphate phases. This new compound has been characterized to have the formula, $(Ca_{1-w}A_w)_i[(P_{1-x-y-z}B_xC_yD_zO_j)]_2$, wherein A is selected from those elements having an ionic radius of approximately 0.4 to 1.1 Å; B, C and D are selected from those elements having an ionic radius of approximately 0.1 to 0.4 Å; w is greater than or equal to zero but less than 1; x is greater than or equal to zero but less than 1; y is greater than or equal to zero but less than 1; z is greater than or equal to zero but less than 1; x + y + z is greater than zero but less than 1; i is greater than or equal to 2 but less than or equal to 4; and j equals 4 - δ , where δ is greater than or equal to zero but less than or equal to 1. The terms w and δ may be selected to provide charge compensation of the elements present in the compound.

An important processing step involves the intimate mixing of silicon as a candidate additive with the particles of the colloidal suspension to ensure the local availability of reactants. This in combination with the similarity of the silicon and phosphorous ionic radii, creates an environment favorable for silicon substitution at phosphorous sites within the Ca-P lattice and the development of the silicon-stabilized TCP structure.

The unique composition does not occur in the absence of intimate mixing as the effect of added silicon in these circumstances is only to influence the activity of CaO as an HA decomposition product. Similarly, the use of additives comprised of larger ions, such as titanium, cannot be accommodated in the lattice at phosphorous sites thereby precluding the important phosphate substitution phenomenon. In both of these cases, the resulting product is predictably β -TCP.

In view of the ability of Skelite™ to participate in the natural bone remodeling process, significant opportunities exist for the development of synthetic bone grafts and bone repair products that are indeed bioactive.

Synthetic Bone Graft Applications

5 A synthetic bone graft that comprises in whole or in part the novel compound of the present invention has numerous applications in the orthopedic industry. In particular, there are applications in the fields of trauma repair, spinal fusion, reconstructive surgery, maxillo-facial surgery and dental surgery.

10 The gold standard in the industry for treating traumatized bone is an autologous bone graft, commonly referred to as an autograft. Autograft transplants involve a surgical procedure in which healthy bone is taken from an alternate part of the patient's skeleton to repair areas of skeletal trauma. Autografts however, require double surgical procedures; one for graft removal and a second for re-implantation at the damaged site. This makes the procedure very expensive and time consuming. Additionally, it is not
15 uncommon for patients to subsequently suffer chronic pain at the autograft harvest site.

 Another widely used bone graft technique is the use of allograft, a term referring to a tissue graft from another individual or animal. In this situation, bone is removed from the donor and implanted in the patient. Allografts are susceptible to various negative consequences. For example, the use of allograft from an animal other than a
20 human carries the possibilities of cross species infection and immunological rejection. Even human sourced allograft, which is used more often than animal tissue, exposes the implant recipient to the possibilities of rejection and disease.

 The use of Skelite™ eliminates the pain and costs associated with the bone harvest procedure required in autograft transplants. Furthermore, since Skelite™ is
25 generated in a laboratory and is completely synthetic, it removes the possibility of transmission of infection and disease, as well as eliminates sources of immunological rejection by the patient.

 Skelite™ fulfils the need for a versatile bone reconstruction material. Its ability to immediately stimulate local natural bone growth provides stability and rapid
30 integration, while the body's normal cell-based bone remodeling process slowly resorbs and replaces the implant with natural bone. This removes the concerns of long term compatibility and durability associated with current artificial implant technologies.

 Products formed from Skelite™ will involve different configurations in order to address the requirements of particular applications. For example, Skelite™-based
35 products can be manufactured as a fine or coarse powder, pellets, shaped three dimensional pieces, macroporous structures, thin films and coatings. In addition, these

products could potentially carry an integrated bone growth factor to speed short term recovery.

5 The use of Skelite™ in a macroporous configuration allows the open porous structure to serve as a scaffold for the integration of new bone tissue. The macroporous structure is formed by the coating of the compound onto a reticulated polymer and subsequently removing the polymer through pyrolysis. The macroporous structure comprises an open cell construction with interconnected voids having a pore size of approximately 50 to 1000 micron. Due to this design, Skelite™ is the ideal bone substitute for implantation at defect sites where special measures are required to encourage new bone growth to bridge areas of major tissue loss due to trauma or surgical intervention. The Applicant has identified two primary approaches for the clinical use of such a product: direct implantation and tissue engineering.

Direct Implantation

15 The simplest approach is to directly implant the Skelite™ scaffold at the location of skeletal trauma where the bioactive properties of the biomaterial compound stimulate the body's natural bone repair mechanism. Once the initial healing process is complete, the Skelite™ scaffold is progressively replaced with natural bone as part of the body's orderly remodeling process.

20 Hybrid versions of Skelite™-based products are possible where bone growth factors are incorporated into the scaffold as a post-manufacturing process or at the time of surgery. The availability of the growth factor at the repair site increases the rate of new bone formation thereby improving patient recovery time and lowering overall health care costs.

25

Tissue Engineering

The concept that underlies the tissue engineering application is to remove bone cells from the patient's skeleton using an established bone marrow aspiration technique, and then carefully introduce the collected cells (cell seeding) into the open cell structure of the Skelite™ scaffold in a sterile biotechnology facility. The cells and scaffold are then incubated so that the cells have an opportunity to multiply and begin to fill the scaffold with new mineralized matrix. After several weeks, the biological implant is ready for implantation back into the patient. This biotechnology bone growth process is termed "tissue engineering", and the procedure serves to enhance the ability of surgeons to reconstruct severely compromised areas of the skeleton. Once successfully integrated at the repair site, the Skelite™ implant is subsequently remodeled into natural bone by the ongoing activity of bone cells.

A refinement of this approach is to selectively extract and grow in cell culture only special precursor cells termed Mesenchymal Stem Cells (MSCs). In order for these cells to remain healthy during biological processing, they need to be attached to a suitable physical carrier. In addition, the performance of the cells benefits from the addition of organic bone growth factors. Skelite™ is a suitable carrier since it allows for both the integration of bone growth factors and the attachment of specialized MSCs. In addition, following implantation and patient recovery, the Skelite™ scaffold is subsequently remodeled into natural bone.

The use of Skelite™ in direct implantation or tissue engineering applications has important advantages over the use of naturally sourced bone graft material, and consequently Skelite™ products have the potential to replace the autograft procedure as the orthopedic surgeon's preferred treatment strategy.

The key advantages of implantable products formed from the Skelite™ material are:

- Immediately stimulates local natural bone growth at the implanted site, thus providing early stability and full integration.
- Ensures long term biocompatibility and efficacy.
- Acts as a bioactive scaffold for use in advanced tissue engineering applications.
- Eliminates the cost and chronic pain associated with the double surgical procedures required in traditional autograft transplants.
- Eliminates the risks of immunological rejection and infection transmission.
- Meets the needs of various orthopedic applications, as the product is available in different configurations.
- Allows for the use of growth factors that can further increase the rate of natural bone healing and subsequent remodeling.
- Provides a means for timed-release drug delivery.
- Disappears naturally through the body's bone remodeling process once therapeutic function is complete.

Drug Carrier Application

The Skelite™ biomaterial may also be used for the incorporation of selected pharmaceuticals into the compound for the further enhancement of the bone healing and remodeling processes. In this respect, pharmaceuticals that have been incorporated into the Skelite™-based products can be predictably released at the site of implantation and hence become available to assist in the bone regeneration process. The Skelite™

biomaterial may also be designed as a slow release vehicle for appropriate pharmaceutical compounds.

Primary candidates for incorporation into Skelite™-based products are selected bone growth factors. These proteins have been identified as being critically important in growing and maintaining healthy bone tissue. In particular, when applied at the site of traumatized bone, natural bone growth is enhanced with a corresponding improvement in overall therapeutic response. However, a compatible carrier system is required to deliver such therapeutic biologicals to the site and ensure local release of appropriate concentrations of the drug. Implant studies have shown that products formed from the Skelite™ biomaterial are suitable for use as drug carriers. One skilled in the art would understand that other pharmaceuticals such as antibiotics for example which may aid in the bone healing process may also be incorporated into the Skelite™ compound.

Coating Applications

Through a liquid application process, the Skelite™ material can be coated on to orthopedic and dental implants to improve and promote natural bone fixation and to improve long term implant stability. Such a coating of approximately 0.1 to 10µm acts at the interface with the patient's own tissue to promote natural bone growth during the weeks immediately following surgery, and is then progressively replaced by the ongoing activity of bone cells once the initial healing process is complete. The result is a strong union between the implant and the host bone. This is not the case with conventional calcium phosphate implant coatings where the biologically inert coating is subject to mechanical detachment (delamination) from the metal substrate, causing potentially catastrophic implant failure.

The key advantages of an implant coating formed from the Skelite™ material are:

- Promotes rapid natural bone growth during the recovery period and is then progressively replaced through the body's orderly remodeling process.
- Eliminates the coating as a potential source of long-term failure and reduces the risk to the patient of incurring complicated and costly revision surgery.
- Reduces patient recovery time and associated health care costs.
- Permits a strong union directly between the implant and the patient's natural bone.
- Involves a manufacturing process based on a liquid application procedure which allows full coverage of the device, including complex surface geometries.

Examples

The examples are described for the purposes of illustration and are not intended to limit the scope of the invention. The examples exemplify aspects of the invention for providing a Skelite™ compound which is an additive stabilized structure having unique physical characteristics and is fully biocompatible with natural bone tissue.

Methods of synthetic chemistry and organic chemistry referred to but not explicitly described in this disclosure and examples are reported in the scientific literature and are well known to those skilled in the art.

Example 1 Preparation of Ca-P Colloidal Suspension (Sol-Gel)

A calcium nitrate solution was created by dissolving 4.72 g of $\text{Ca}(\text{NO}_3)_2$ in 80 mL of a solution of DDH₂O containing approximately 3 mL of 30% NH_4OH .

Similarly, an ammonium phosphate solution was prepared by dissolving 1.38 g of $\text{NH}_4\text{H}_2\text{PO}_4$ in 192 mL of a solution of DDH₂O containing approximately 71 mL of 30% NH_4OH . The pH of the final solutions was approximately 11. The ammonium phosphate solution was added drop-wise into the calcium nitrate solution to form a calcium phosphate precipitate. On completion of the reaction, the solution and precipitate were aged for a period of 24 hours. Following aging, 240 mL of the solution containing the precipitate was centrifuged for 20 minutes at 500 rpm. Without disturbing the sediments, 180 mL of supernatant was discarded from the bottle. The sediments were then re-suspended by rotating the bottle on an orbital shaker for one hour.

The resulting Ca-P colloidal suspension may be used in a variety of further preparations.

Example 2 Preparation of Thin Films

To create a thin film on a transparent substrate, quartz (amorphous silica) substrates were cleaned using water and chromic acid and subsequently dip coated in the colloidal suspension of Example 1. This was achieved by suction mounting the substrates on a computer controlled linear slide. The mounted substrates were lowered into the colloidal suspension and immediately withdrawn at a programmed speed of 2 mm/s. Following dip coating, the substrates were allowed to dry in ambient conditions and were subsequently sintered in a programmable furnace for a

period of 1 hour at temperatures ranging from 800°C to 1000°C. The sintered thin films had a uniform translucent appearance characteristic of a polycrystalline thin film. The thin film had an approximate thickness of 0.5 to 1.0 µm with a particle size on the order of 0.2 to 1.0 µm.

5

Example 3 Preparation of Ca-P Powder with No Introduced Additives

Following the procedures for the formation and aging of the colloidal suspension of Example 1, the colloid was processed to the stage of reducing the volume by centrifugation. The precipitate was dried for approximately 5 hours at 100°C and sintered for one hour in an open alumina crucible in air at a temperature of 1000°C. A fine powder was formed through mechanical grinding of the sintered material in a motorized mortar and pestle (Retsch Model RM 100 USA).

Example 4 Preparation of Ca-P Powder with Silicon as the Introduced Additive

Following the procedures for the formation and aging of the colloidal suspension of Example 1, the colloid was processed to the stage of reducing the volume by centrifugation. In order to retain the colloidal sol characteristics, the silicon additive was introduced as a sol-gel metal-organic precursor in an organic carrier. The precursor was either tetrapropyl orthosilicate ($\text{Si}(\text{OC}_3\text{H}_7)_4$ or TPOS) or tetraethyl orthosilicate ($\text{Si}(\text{OC}_2\text{H}_5)_4$ or TEOS). Addition was accomplished by creating a sol using a precursor carrier such as 2-methoxyethanol ($\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$ or 2Me) or 2-4 pentanedione ($\text{CH}_3\text{COCH}_2\text{COCH}_3$ or ACAC). The action of the carrier was to ensure that the additive did not precipitate upon addition to an aqueous solution having a pH similar to that of the Ca-P colloidal suspension. This ensured that the additive was uniformly mixed within the colloid to create a single precipitate rather than two distinct precipitates. Precipitation of the additive was examined in a separate experiment with aqueous solutions. For the silicon compounds, precipitation was minimal for 2Me, ACAC and even if no carrier was employed. The precipitate with introduced silicon was dried for approximately 5 hours at 100°C and sintered for one hour in an open alumina crucible in air at a temperature of 1000°C. A fine powder was formed through mechanical grinding of the sintered material in a motorized mortar and pestle (Retsch Model RM 100 USA). The presence of the additive within the sintered ceramics was checked by wet chemical analysis.

Example 5 **Preparation of Ca-P Powder with Titanium as the Introduced Additive**

Following the procedures for the formation and aging of the colloidal suspension of Example 1, the colloid was processed to the stage of reducing the volume by centrifugation. In order to retain the colloidal sol characteristics, the titanium additive was introduced as a sol-gel metal-organic precursor in an organic carrier. The precursor was titanium n-propoxide ($\text{Ti}(\text{OC}_3\text{H}_7)_4$). Addition was accomplished by creating a sol using a precursor carrier such as 2-methoxyethanol ($\text{CH}_3\text{OCH}_2\text{CH}_2\text{OH}$ or 2Me) or 2-4 pentanedione ($\text{CH}_3\text{COCH}_2\text{COCH}_3$ or ACAC). ACAC was used in particular for its strong chelating action. Precipitation of the additive was examined in a separate experiment with aqueous solutions. For titanium n-propoxide, precipitation of the additive occurred for both no carrier and 2Me, but not for ACAC. The precipitate with introduced titanium was dried for approximately 5 hours at 100°C and sintered for one hour in an open alumina crucible in air at a temperature of 1000°C . A fine powder was formed through mechanical grinding of the sintered material in a motorized mortar and pestle (Retsch Model RM 100 USA). The presence of the additive within the sintered ceramics was checked by wet chemical analysis.

Example 6 **Preparation of Ceramic Pellets**

Ceramic pellets were formed from previously sintered powder that had been prepared according to Examples 3, 4, or 5, using a small amount of the concentrated colloid suspension mixed into the sintered powder as a binding agent. The powders were uniaxially pressed into pellets with a pressure of $1 \times 10^8 \text{ N/m}^2$ [15,000 psi]. The final pellets were sintered for one hour in air at a temperature of 1000°C to create ceramic components with the desired characteristics. Following thermal processing, the pellet density was approximately 1.5 g/cm^3 , and the pellet exhibited a uniform microporosity throughout the structure.

Example 7 **Preparation of Macroporous Structures**

Sintered powder that had been prepared according to Examples 3, 4, or 5, was sieved using a motorized sieve shaker (Retsch Model AS200 BASIC USA). Powder having a particle size of -325 Mesh was collected and subsequently suspended in water to form a slurry. The interior and exterior surfaces of a preformed piece of open

cell (reticulated) polyurethane foam were completely coated by immersing the foam in the slurry. The slurry-coated component was then allowed to dry and was subsequently sintered at 1000°C for 1 hour. During thermal processing, the foam was removed from the structure through pyrolysis. Importantly, the shape of the final ceramic component replicates the original shape of the foam, including the open-cell structure.

In the preparation of these components, the pore density of the foam was selected to produce the required pore size in the ceramic. Typical pore sizes prepared were in the range of 45 to 80 pores per inch. The coating of the foam was managed to ensure complete coverage of the foam without clogging of the cells. The duration and temperature of the thermal processing were selected to ensure pyrolysis of the foam and to obtain the desired physical properties of the resulting macroporous structure.

Example 8 Preparation of Drug Carrier with Associated Pharmaceutical Agent

Depending on application requirements, either the powder of Example 4 or the macroporous structure of Example 7 was sterilized using ethylene oxide or similar approved medical device sterilization technique. In a laminar flow hood, a liquid drug volume was made up according to dosing requirements. In the case of the agent BCSF™ (Bone Cell Stimulating Factor), this required addition of sterile normal saline (0.9 % NaCl) to previously lyophilized stored aliquots of the drug, at room temperature. Following reconstitution, the drug was either mixed by gentle agitation with the powder, or slowly dispensed over the surface of the macroporous structure.

Recognizing the natural protein avidity of the bioceramic material, a period of 5 minutes was allowed for the drug to percolate and bind to either the powder or the macroporous structure. Following this period, the preparation was ready for direct patient administration as a therapeutic device or for use as a tissue-engineering scaffold.

In the case of therapeutic administration of the powder-based preparation, a predetermined volume of the suspension (powder plus attached pharmaceutical agent) was injected percutaneously at the desired skeletal site.

In the case of therapeutic administration of macroporous structures, surgical intervention was required to implant the device at skeletal sites in order to effect subsequent bone repair.

Example 9 Commercial Reference Materials

The commercially available HA (cHA), α -TCP, β -TCP, calcium silicate and silica materials listed in Table 1 (below) were used as reference standards for the analytical techniques performed in the evaluation of the internally prepared mHA and Si-mHA materials described in this study.

| Table 1: List of Materials Used For Experimental Samples and Reference Standards | | |
|--|--------------------|---|
| <i>Commercial Materials</i> | | <i>Source</i> |
| Commercial HA | cHA | Aldrich #28,939-6 Lot#04302TQ |
| α -TCP | α -TCP | Supelco Inc #3-3910 Lot#200792 |
| β -TCP | β -TCP | Fluka #21218 Analysis#357352/1 14996 |
| Calcium silicate | CaSiO ₃ | Aldrich #37,266-8 Lot#00714LN |
| Silica | SiO ₂ | PPG Industries Inc. #63231674 Lot#9-134 |

| <i>Internally Prepared Materials</i> | | <i>Preparation Technique</i> |
|--------------------------------------|--------|--|
| Microporous HA | mHA | Powder prepared from the thermal processing of the colloid in equation (1) |
| Si-TCP + mHA | Si-mHA | Powder prepared from the thermal processing of the colloid in equation (1) where Si is the introduced additive |

10 **Example 10 Analytical Techniques**

X-ray diffraction (XRD) spectra of thin films were acquired using a glancing angle (GA-XRD) technique with an angle of incidence $\theta = 2^\circ$, whereas powders were examined using conventional θ -2 θ geometry. The source was a 12 kW Rigaku rotating anode XRD generator fitted with a Cr target for improved peak resolution. The glancing angle geometry significantly reduced the contribution from the substrate. For convenience of comparison to other literature, all spectra were converted to that expected for a Cu anode using the following relationship: $\sin(\theta_{Cu}) = (\lambda_{Cu}/\lambda_{Cr})\sin(\theta_{Cr})$, where $\lambda_{Cu} = 1.54056 \text{ \AA}$ and $\lambda_{Cr} = 2.28970 \text{ \AA}$. The phase composition was determined by comparing acquired spectra with peaks identified in the Joint

Committee on Powder Diffraction Standards (JCPDS) database of standards [20]. Of particular relevance to this study are the XRD spectra of HA (JCPDS #9-432), α -TCP (JCPDS #9-348) and β -TCP (JCPDS #9-169). Following the collection of XRD data, the background noise was subtracted and the integrated intensities of peaks

5 distinguishable as HA, α -TCP or β -TCP were calculated. These values were then used to determine the percentage phase composition (plus or minus 5%).

Optical microscopy, scanning electron microscopy (SEM, using a JEOL JSM 840) and transmission electron microscopy (TEM, using a Philips CM20) were performed to assess the surface and bulk morphology. Chemical analysis of the
10 samples was carried out by wet chemical methods and neutron activation analysis. Wide-line nuclear magnetic resonance (NMR) experiments on ^{29}Si were accomplished using a Bruker NMR CXP 200 MHz spectrometer with magic angle spinning using a pulse width of 5 ms and a pulse delay of 20 s. Infrared spectroscopy (IR) of powders using a KBr pellet technique utilized a BOMEM MB-120 spectrometer.
15 Approximately 2 mg of sample and approximately 200 mg of KBr were ground and pressed in a 6 mm diameter die at 10 tonnes for 1 minute to produce uniform discs for analysis.

A particle size analysis of the Ca-P colloid at various stages of processing was made by observation of 633 nm He-Ne laser light scattered at various angles.
20 Samples were prepared by adding 10 drops of the precipitated solution to 4 mL ammoniated water (one part 30% NH_4OH mixed with five parts water) having a pH greater than 10. Results from these suspensions were reproducible for equivalent samples and stable over time. The power spectrum of the scattered light at a known angle was fitted to a Lorentzian distribution and analyzed by standard methods using a
25 solution viscosity of $8.9 \times 10^4 \text{ kg m}^{-1}\text{s}^{-1}$ and refractive index of 1.3312 [21,22].

Although preferred embodiments have been described herein in detail, it is understood by those skilled in the art that variations may be made thereto without departing from the scope of the invention as defined by the appended claims.
30

Table 2: Summary of Effective Ionic Radius and Ionic Crystal Radius for Various Elements

5 Data from: Shannon, R.D., Acta Cryst. (1976) A32, 751

| <i>Ion</i> | <i>Coordination Number (CN)</i> | <i>Ionic Crystal Radius (CR)</i> | <i>Effective Ionic Radius (IR)</i> |
|------------|-------------------------------------|--------------------------------------|--|
| B^{3+} | 4 | 0.25 | 0.11 |
| | 6 | 0.41 | 0.27 |
| Ba^{2+} | 6 | 1.49 | 1.35 |
| | 8 | 1.56 | 1.42 |
| Ca^{2+} | 6 | 1.14 | 1.00 |
| | 8 | 1.26 | 1.12 |
| Ce^{3+} | 6 | 1.15 | 1.01 |
| | 8 | 1.28 | 1.14 |
| La^{3+} | 6 | 1.17 | 1.03 |
| | 8 | 1.30 | 1.16 |
| Mg^{2+} | 4 | 0.71 | 0.57 |
| | 6 | 0.86 | 0.72 |
| | 8 | 1.03 | 0.89 |
| P^{5+} | 4 | 0.31 | 0.17 |
| | 6 | 0.52 | 0.38 |
| Sc^{3+} | 6 | 0.89 | 0.75 |
| | 8 | 1.01 | 0.87 |
| Si^{4+} | 4 | 0.40 | 0.26 |
| | 6 | 0.54 | 0.40 |
| Ti^{4+} | 4 | 0.56 | 0.42 |
| | 6 | 0.75 | 0.61 |
| | 8 | 0.88 | 0.74 |
| Y^{3+} | 6 | 1.04 | 0.90 |
| | 8 | 1.16 | 1.02 |
| Zr^{4+} | 4 | 0.73 | 0.59 |
| | 6 | 0.86 | 0.72 |
| | 8 | 0.98 | 0.84 |

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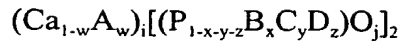
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- 20 33. Keller, L., P. Rey-Fessler. *Characterization and Performance of Calcium Phosphate Coatings for Implants* edited by E. Horowitz and J. Parr. Philadelphia: ASTM, pp. 54-62 (1994).
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We claim:

1. A biomaterial compound comprising calcium, oxygen and phosphorous, wherein at least one of said elements is substituted with an element having an ionic
5 radius of approximately 0.1 to 1.1Å.
2. The biomaterial compound as claimed in claim 1, wherein a portion of the phosphorous is substituted by at least one element having an ionic radius of approximately 0.1 to 0.4Å.
10
3. The biomaterial compound as claimed in claim 1 or 2, wherein said element of substitution is silicon.
4. The biomaterial compound as claimed in claim 1 or 2, wherein said element of
15 substitution is boron.
5. The biomaterial compound as claimed in claim 2, wherein said compound additionally comprises at least one element selected from elements having an ionic radius from approximately 0.4 to 1.1Å, wherein said additional elements substitute at
20 sites other than phosphorous.
6. The biomaterial compound as claimed in claim 5, wherein said element has an effective charge to compensate any imbalance of charge resulting from the partial substitution of phosphorous.
25
7. The biomaterial compound as claimed in any one of claims 1 to 6 in combination with at least one calcium phosphate material selected from the group consisting of calcium hydroxyapatite, α -TCP, β -TCP, octocalcium phosphate, tetracalcium phosphate, dicalcium phosphate and calcium oxide.
30
8. The biomaterial compound as claimed in claim 7 wherein said compound is mixed with calcium hydroxyapatite in a ratio of approximately 20:80 to 80:20.
9. The biomaterial compound as claimed in claim 2 or 3 wherein said compound
35 is defined by those peaks in the x-ray diffraction spectrum of Figure 16.
10. A biomaterial compound having the formula:



wherein A is selected from those elements having an ionic radius of approximately 0.4 to 1.1 Å;

5 B, C and D are selected from those elements having an ionic radius of approximately 0.1 to 0.4 Å;

w is greater than or equal to zero but less than 1;

x is greater than or equal to zero but less than 1;

y is greater than or equal to zero but less than 1;

z is greater than or equal to zero but less than 1;

10 x + y + z is greater than zero but less than 1;

i is greater than or equal to 2 but less than or equal to 4; and

j equals 4-δ, where δ is greater than or equal to zero but less than or equal to 1.

11. The biomaterial compound as claimed in claim 10, wherein w and δ are
15 determined by charge compensation of the elements present in the compound.

12. The biomaterial compound as claimed in claim 10, wherein B is silicon.

13. The biomaterial compound as claimed in claim 10, wherein B is boron.
20

14. The biomaterial compound as claimed in claim 11, wherein A is selected from
the group of elements consisting of Ce, La, Sc, Y and Zr.

15. The biomaterial compound as claimed in any one of claims 10 to 14 in
25 combination with at least one calcium phosphate material selected from the group
consisting of calcium hydroxyapatite, α-TCP, β-TCP, octocalcium phosphate,
tetracalcium phosphate, dicalcium phosphate and calcium oxide.

16. The biomaterial compound as claimed in claims 1 or 10 wherein said
30 compound additionally comprises an additive to increase the mechanical toughness
and strength of said compound.

17. The biomaterial compound as claimed in claim 16 wherein said additive is of a
material comprising discrete particles of a size removable by phagocytosis by the
35 action of macrophages.

18. The biomaterial compound as claimed in claim 17 wherein said additive

comprises micro carbon fibers.

19. The biomaterial compound as claimed in claims 1 or 10, wherein said compound is $\text{Ca}_3(\text{P}_{0.750}\text{Si}_{0.25}\text{O}_{3.875})_2$.

5

20. The biomaterial compound as claimed in claims 1 or 10, wherein said compound is $\text{Ca}_3(\text{P}_{0.9375}\text{Si}_{0.0625}\text{O}_{3.96875})_2$.

21. The biomaterial compound as claimed in claim 7 or 15 wherein said combination exists as a physical mixture.

10

22. The biomaterial compound as claimed in claim 7 or 15 wherein said combination exists as a solid solution.

23. The biomaterial compound as claimed in claims 1 or 10 wherein said compound has a microporous structure.

15

24. The biomaterial compound as claimed in claims 21 or 22, wherein said combination has a microporous structure.

20

25. The biomaterial compound as claimed in claim 23 or 24, wherein said microporous structure comprises particles in the size range of approximately 0.1 to 2.0 microns.

26. The biomaterial compound as claimed in any one of claims 1 to 25 wherein said compound is formed as a macroporous structure comprising an open cell construction with interconnected voids having a pore size of approximately 50 to 1000 microns.

25

27. The biomaterial compound as claimed in claim 26 wherein said macroporous structure is formed by coating said compound onto a reticulated polymer and subsequently removing said polymer through pyrolysis.

30

28. The biomaterial compound as claimed in any one of claims 1 to 27, wherein said compound has a nanoporous structure.

35

29. The biomaterial compound as claimed in claim 28 wherein said nanoporous structure comprises granules in the size range of approximately 1 to 20nm.

30. The biomaterial compound as claimed in claims 1 or 10 wherein said compound has monoclinic pseudo-rhombic symmetry.
- 5 31. The biomaterial compound as claimed in claims 1 or 10 wherein said compound is in the monoclinic space group $P2_1/a$.
32. The biomaterial compound as claimed in any one of claims 1 to 31, wherein said compound is resorbed by the cellular activity of osteoclasts.
- 10 33. The biomaterial compound as claimed in any one of claims 1 to 31, wherein said compound promotes the generation of new mineralized bone matrix by the activity of osteoblasts.
- 15 34. The biomaterial compound as claimed in any one of claims 1 to 31 wherein said compound is progressively replaced with natural bone *in vivo*.
35. The biomaterial compound as claimed in claims 1 or 10 wherein said compound is essentially insoluble in biological media at human physiological pH of
- 20 6.4-7.3.
36. The biomaterial compound as claimed in claims 1, 7, 10 or 15 in combination with collagen.
- 25 37. The use of the biomaterial compound as claimed in any one of claims 1 to 36 in orthopedic, maxillo-facial and dental applications wherein said compound exists as a fine or coarse powder, pellets, three-dimensional shaped pieces, macroporous structures, thin films and coatings.
- 30 38. The use of the biomaterial compound as claimed in any one of claims 1 to 36 as a coating of thickness 0.1 to 10 microns on implantable prostheses.
39. The use of the biomaterial compound as claimed in any one of claims 1 to 36 in tissue engineering.
- 35 40. The use of the biomaterial compound as claimed in any one of claims 1 to 36 as a carrier for pharmaceutical agents.

41. The use of the biomaterial compound as claimed in claim 40, wherein said compound acts as a slow release vehicle for pharmaceuticals at desired sites of implantation.

5

42. The use of the biomaterial compound as claimed in claim 41 wherein said pharmaceutical is a bone growth factor.

43. A method for substituting natural bone at sites of skeletal surgery in human and animal hosts with a biomaterial compound comprising calcium, oxygen and phosphorous wherein at least one of said elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1 Å;

10 said method comprising the steps of:
implanting said biomaterial compound at the site of skeletal surgery wherein
15 such implantation promotes the formation of new bone tissue at the interfaces between said biomaterial compound and said host, the progressive removal of said biomaterial compound primarily through osteoclast activity, and the replacement of that portion of said biomaterial compound removed by further formation of new bone tissue by osteoblast activity, such progressive removal and replacement being inherent in the
20 natural bone remodeling process.

44. A method for repairing large segmental skeletal gaps and non-union fractures arising from trauma or surgery in human and animal hosts using a biomaterial compound comprising calcium, oxygen and phosphorous wherein at least one of said
25 elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1 Å;

said method comprising the steps of:
implanting said biomaterial compound at the site of the segmental skeletal gap or non-union fracture wherein such implantation promotes the formation of new bone
30 tissue at the interfaces between said biomaterial compound and said host, the progressive removal of said biomaterial compound primarily through osteoclast activity, and the replacement of that portion of said biomaterial compound removed by further formation of new bone tissue by osteoblast activity, such progressive removal and replacement being inherent in the natural bone remodeling process.

35

45. A method for aiding the attachment of implantable prostheses to skeletal sites and for maintaining the long term stability of said prostheses in human and animal

hosts using a biomaterial compound comprising calcium, oxygen and phosphorous wherein at least one of said elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1Å;

said method comprising the steps of :

- 5 coating selected regions of an implantable prosthesis with said biomaterial compound, implanting said coated prosthesis into a skeletal site wherein such implantation promotes the formation of new bone tissue at the interfaces between said biomaterial compound and said host, the generation of a secure interfacial bond between said host bone and said coating, the subsequent progressive removal of said
- 10 coating primarily through osteoclast activity such that the coating is diminished, and the replacement of that portion of said biomaterial compound removed by further formation of new bone tissue to generate a secure interfacial bond directly between said host bone and said prosthesis.

- 15 46. A method for providing tissue-engineering scaffolds for bone replacement in human or animal hosts using a biomaterial compound comprising calcium, oxygen and phosphorous wherein at least one of said elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1Å;

said method comprising the steps of :

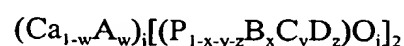
- 20 forming said biomaterial compound as a macroporous structure comprising an open cell construction with interconnected voids, combining mature and/or precursor bone cells with said macroporous structure, and allowing the cells to infiltrate said structure in order to develop new mineralized matrix throughout said structure.

- 25 47. A method for delivering pharmaceutical agents to the site of skeletal surgery in human or animal hosts using a biomaterial compound comprising calcium, oxygen and phosphorous wherein at least one of said elements is substituted with an element having an ionic radius of approximately 0.1 to 1.1Å;

said method comprising the steps of :

- 30 combining a pharmaceutical agent with said biomaterial compound and applying the pharmaceutical agent combined with said biomaterial compound to a site of skeletal surgery, wherein such application results in controlled local release of said pharmaceutical agent.

- 35 48. The method of any one of claims 43 to 47 wherein said biomaterial compound has the formula;



wherein A is selected from those elements having an ionic radius of approximately 0.4 to 1.1 Å;

B, C and D are selected from those elements having an ionic radius of approximately 0.1 to 0.4 Å;

5 w is greater than or equal to zero but less than 1;

x is greater than or equal to zero but less than 1;

y is greater than or equal to zero but less than 1;

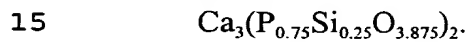
z is greater than or equal to zero but less than 1;

x + y + z is greater than zero but less than 1;

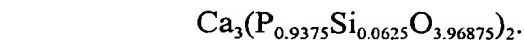
10 i is greater than or equal to 2 but less than or equal to 4; and

j equals 4-δ, where δ is greater than or equal to zero but less than or equal to 1.

49. The method of any one of claims 43 to 48 wherein said biomaterial compound has the formula:



50. The method of any one of claims 43 to 48 wherein said biomaterial compound has the formula:



51. The method of any one of claims 43 to 50 wherein said biomaterial compound is combined with at least one calcium phosphate material selected from the group consisting of calcium hydroxyapatite, α-TCP, β-TCP, octocalcium phosphate, tetracalcium phosphate, dicalcium phosphate and calcium oxide.

25

52. The method of any one of claims 43 to 51, wherein said biomaterial compound additionally comprises an additive to increase the mechanical toughness and strength of said compound.

FIGURE 1

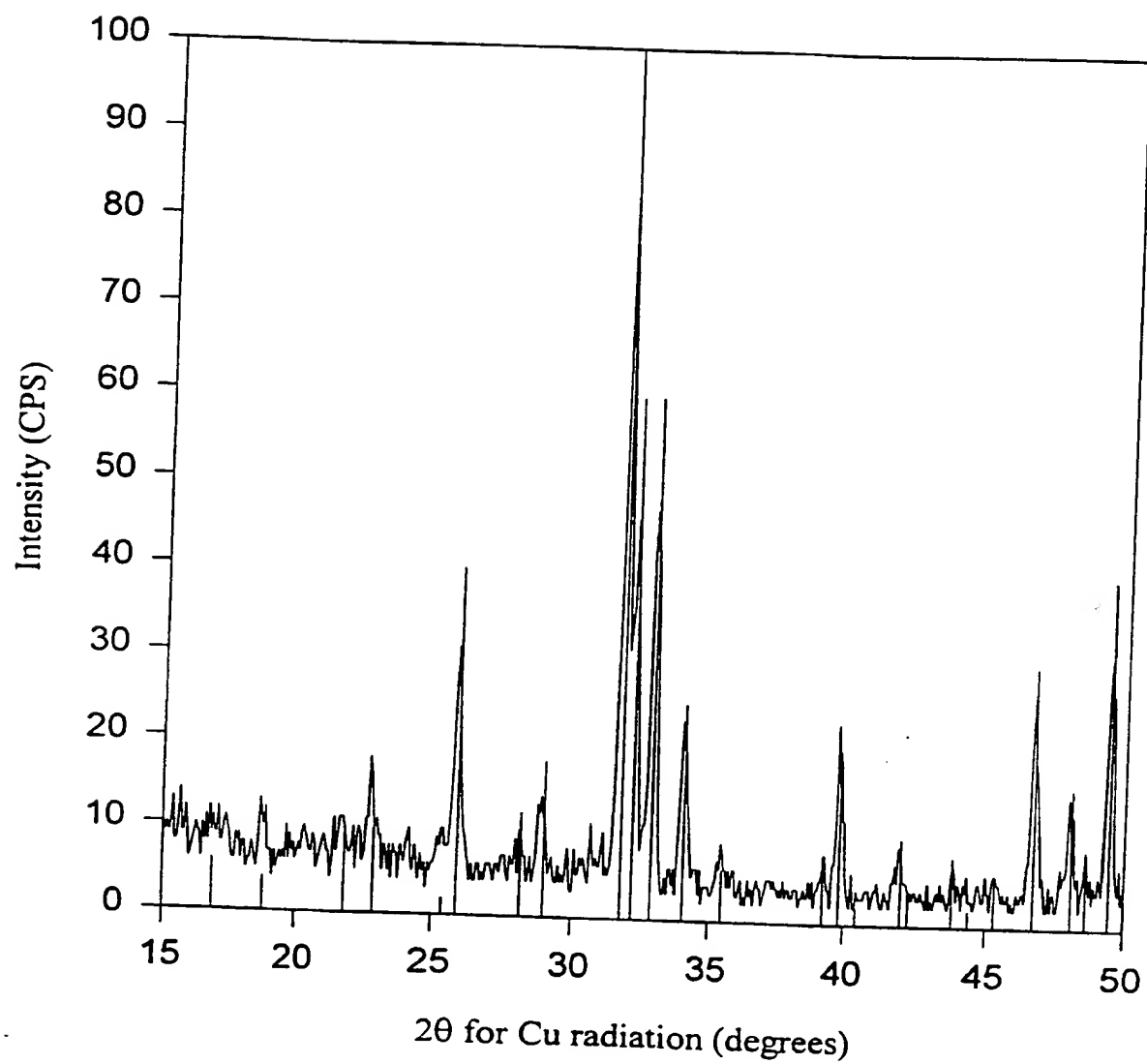


FIGURE 2

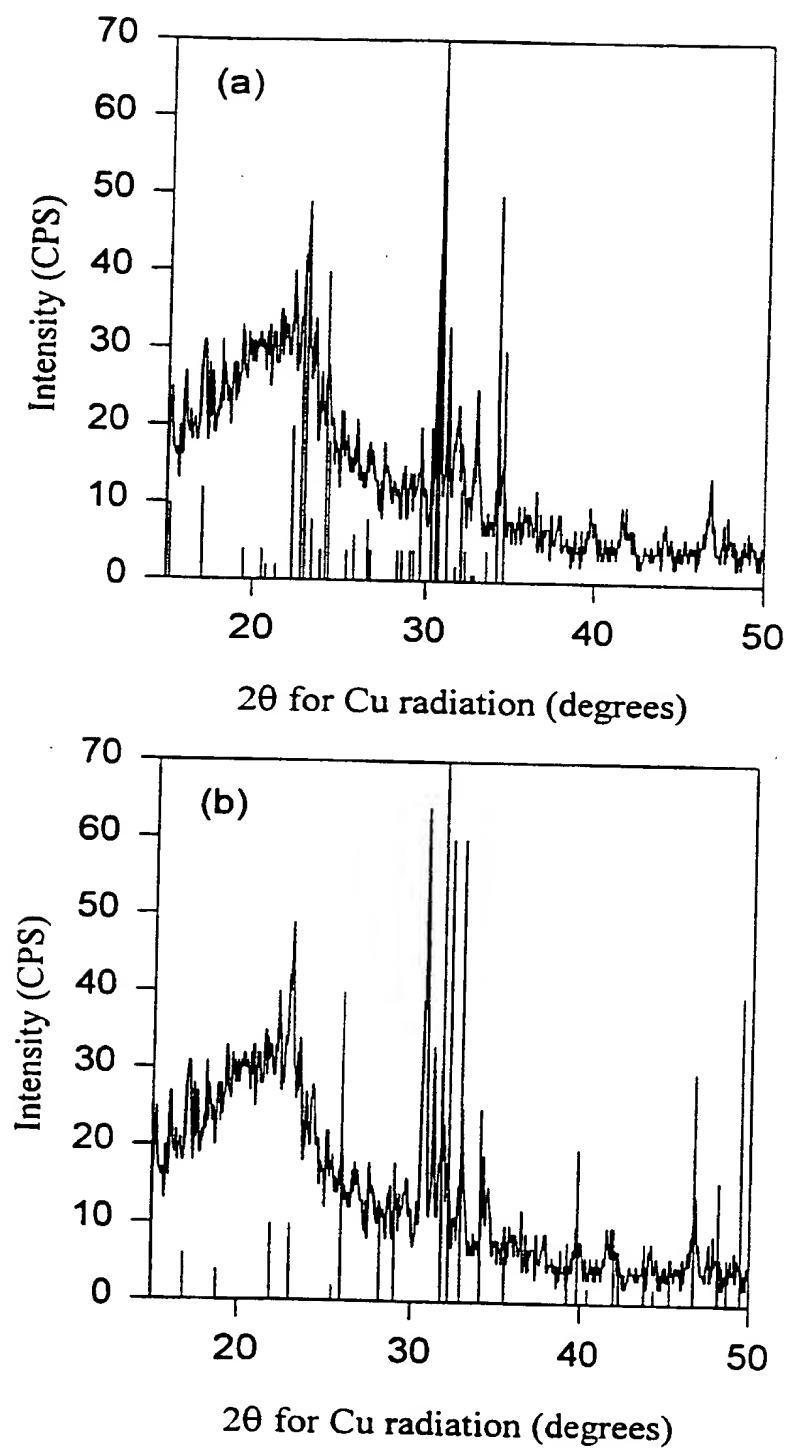


FIGURE 3

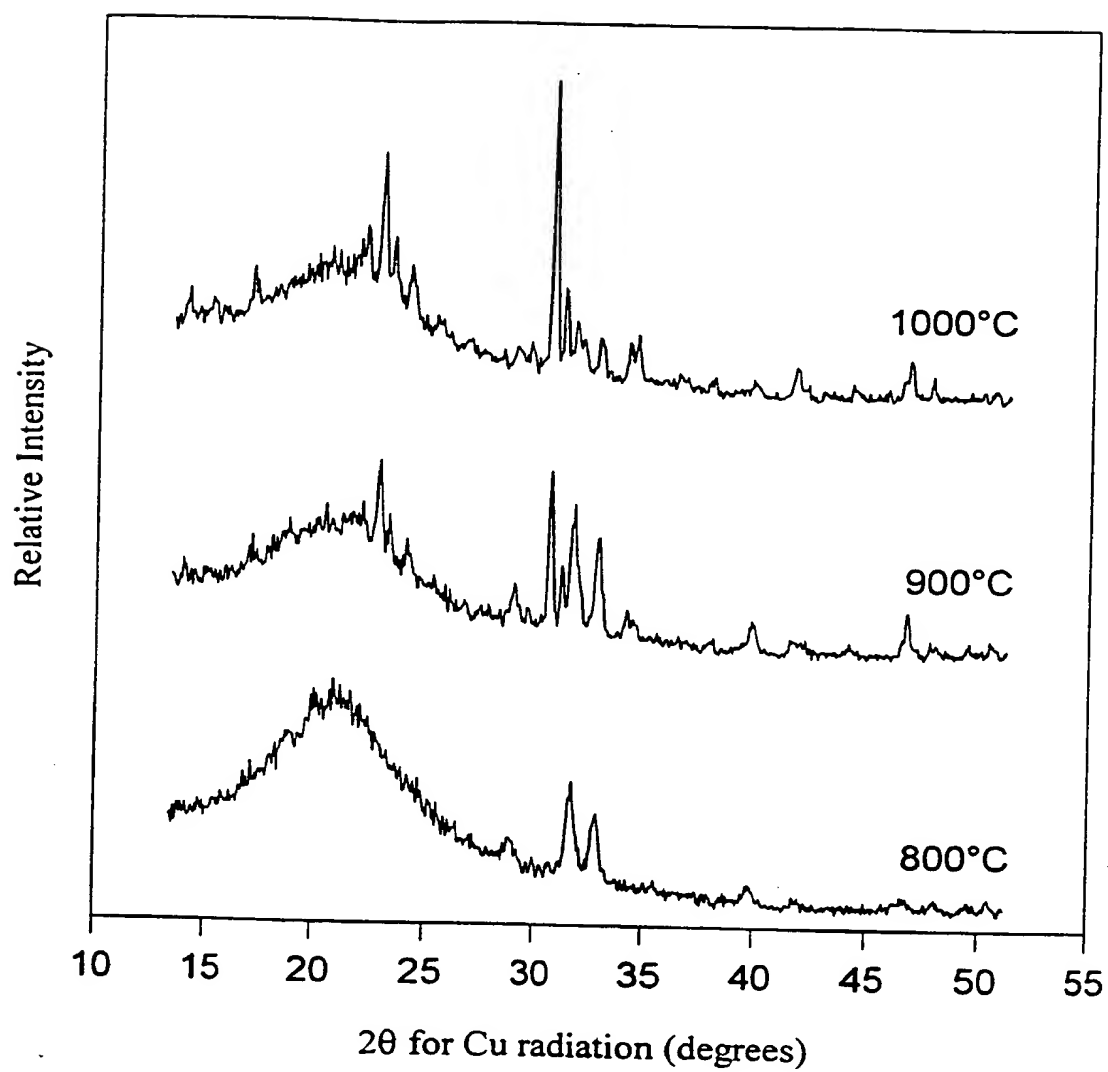


FIGURE 4

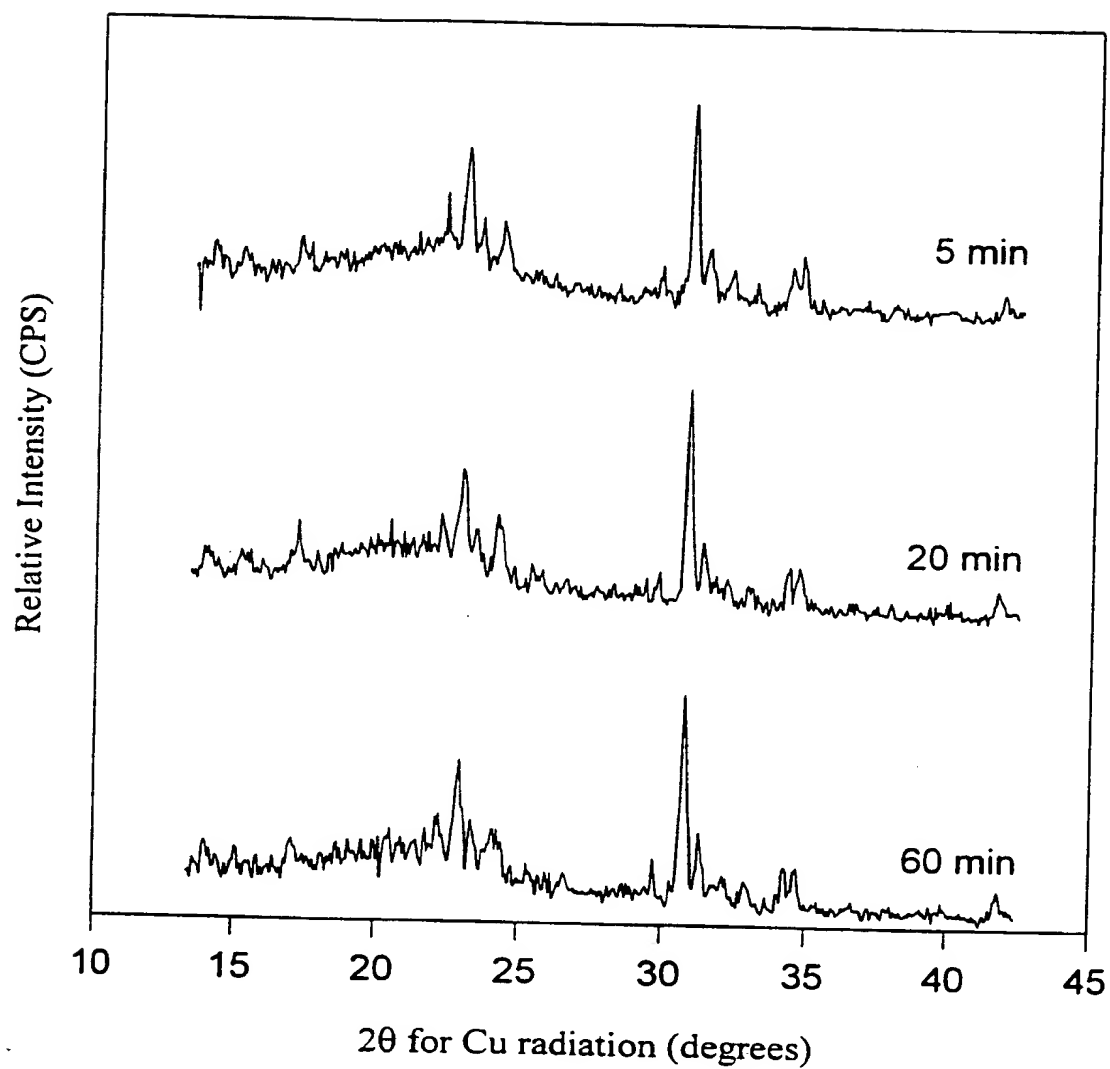


FIGURE 5

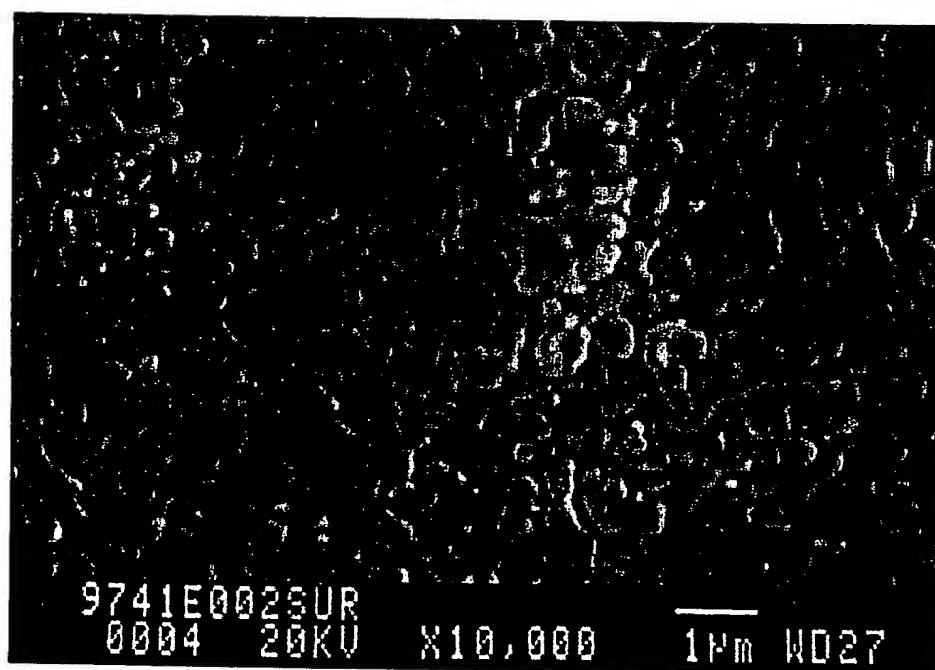


FIGURE 6

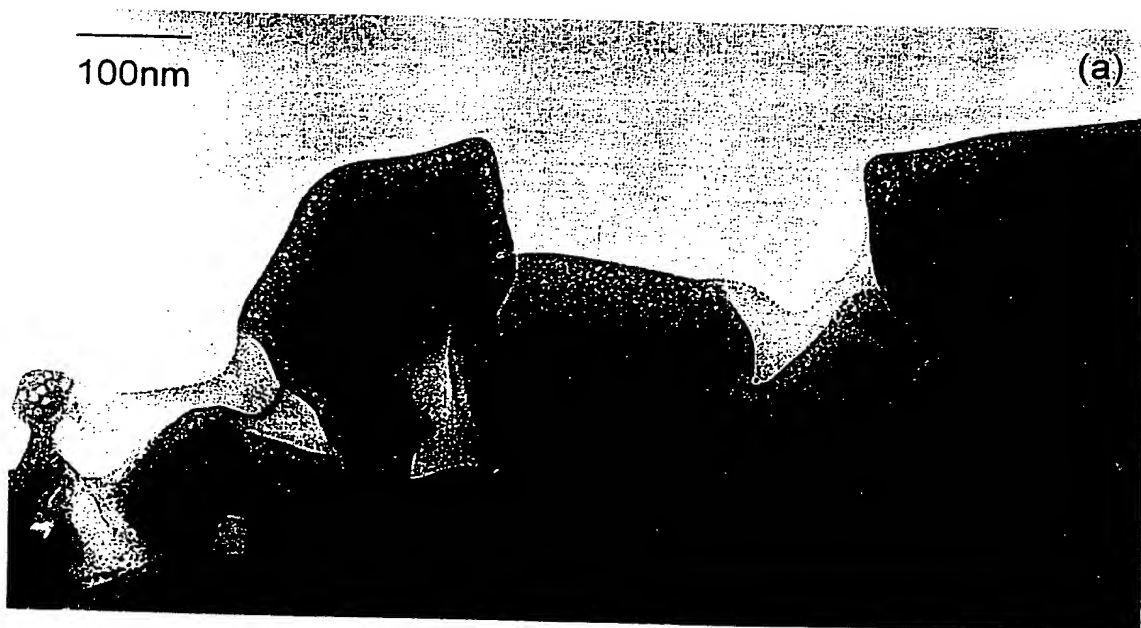


FIGURE 7

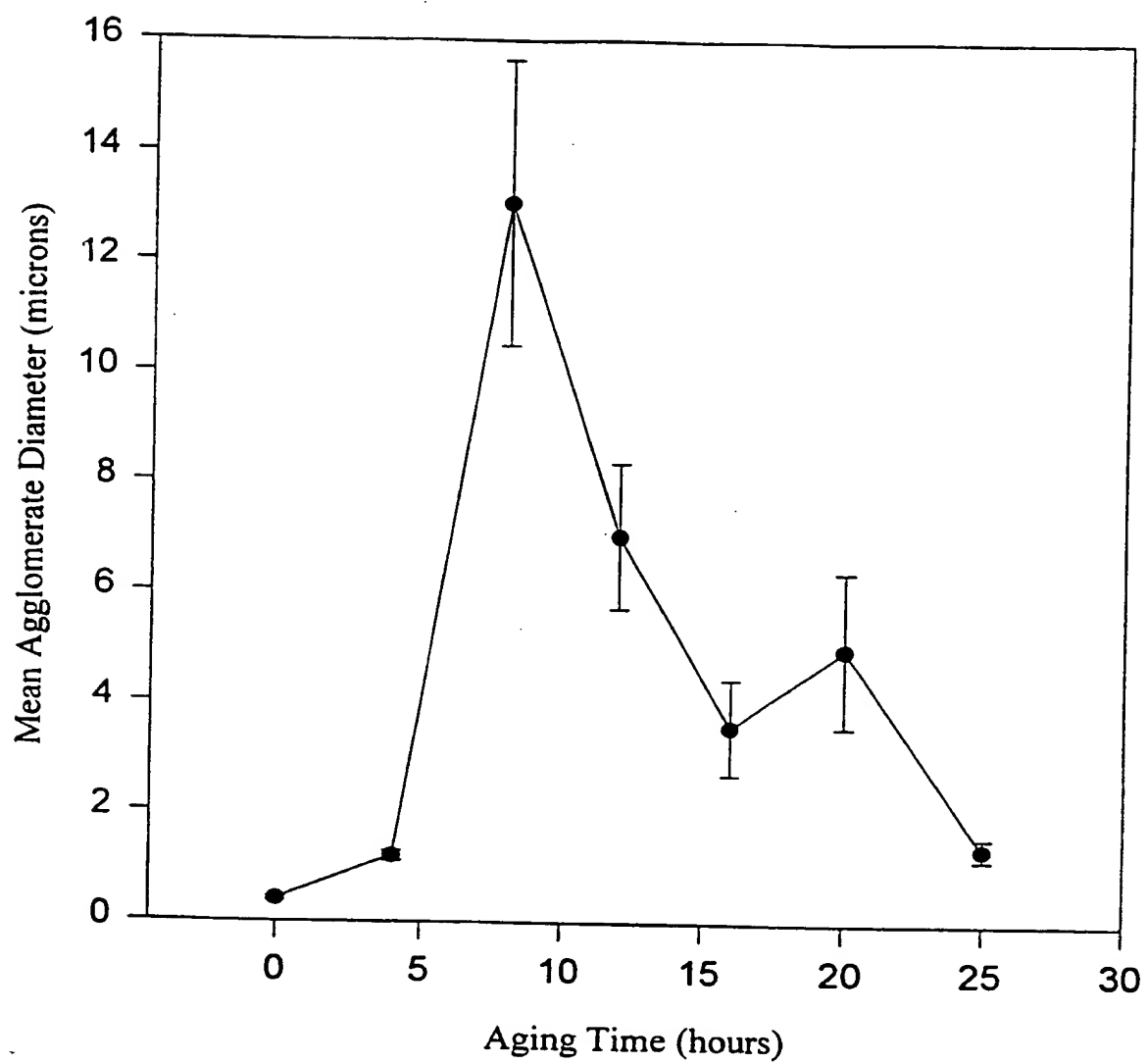


FIGURE 8

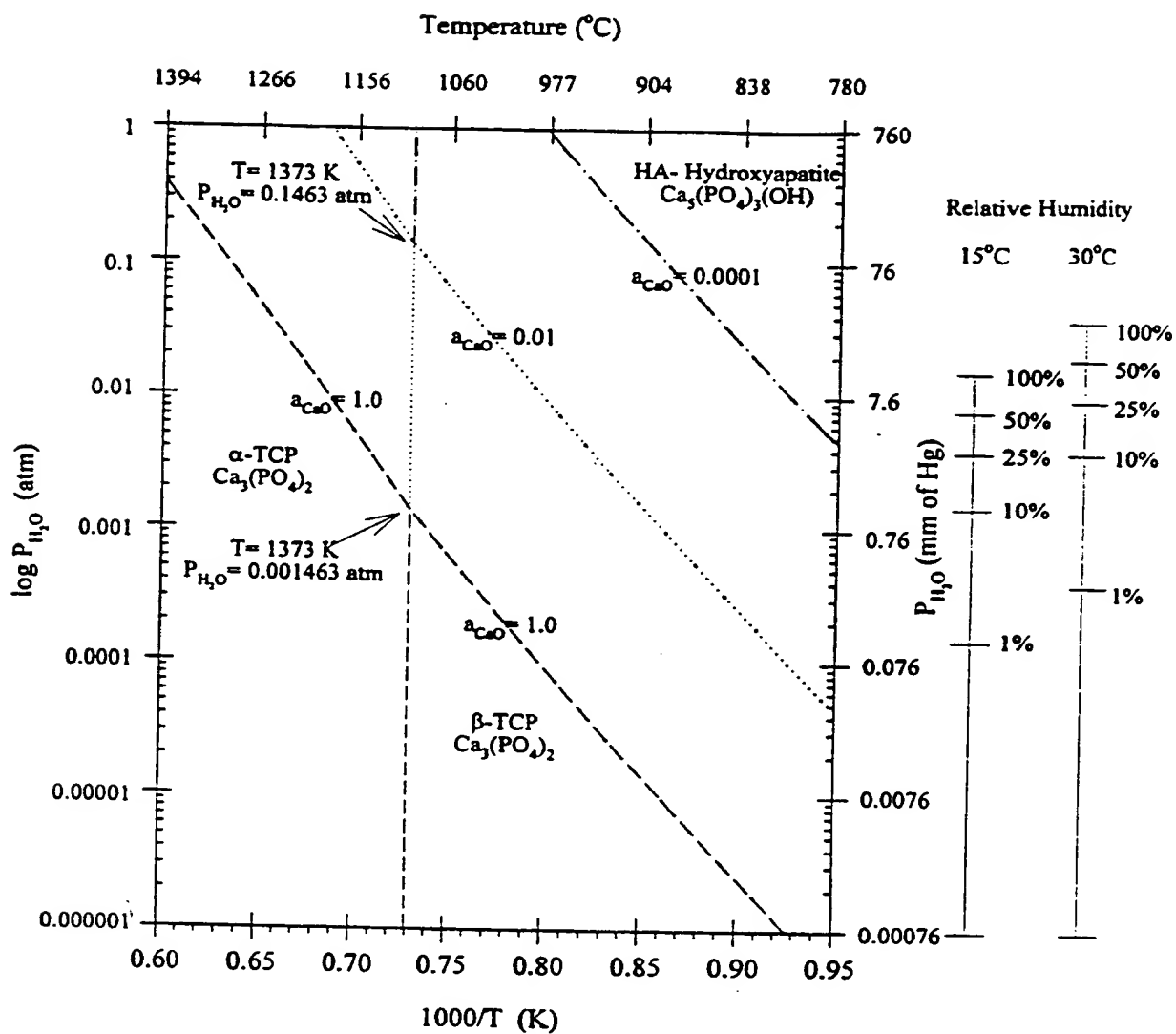


FIGURE 9

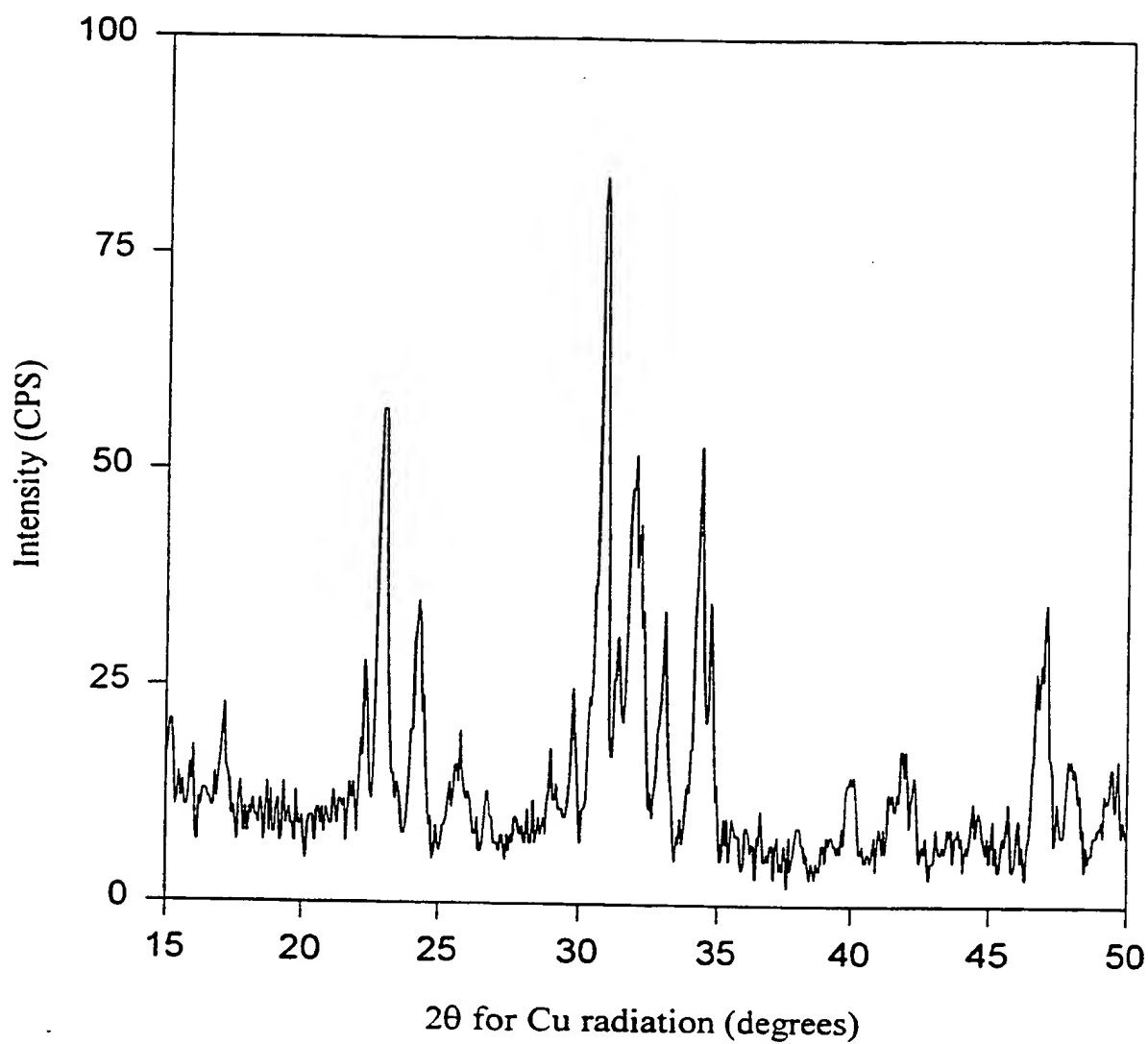


FIGURE 10

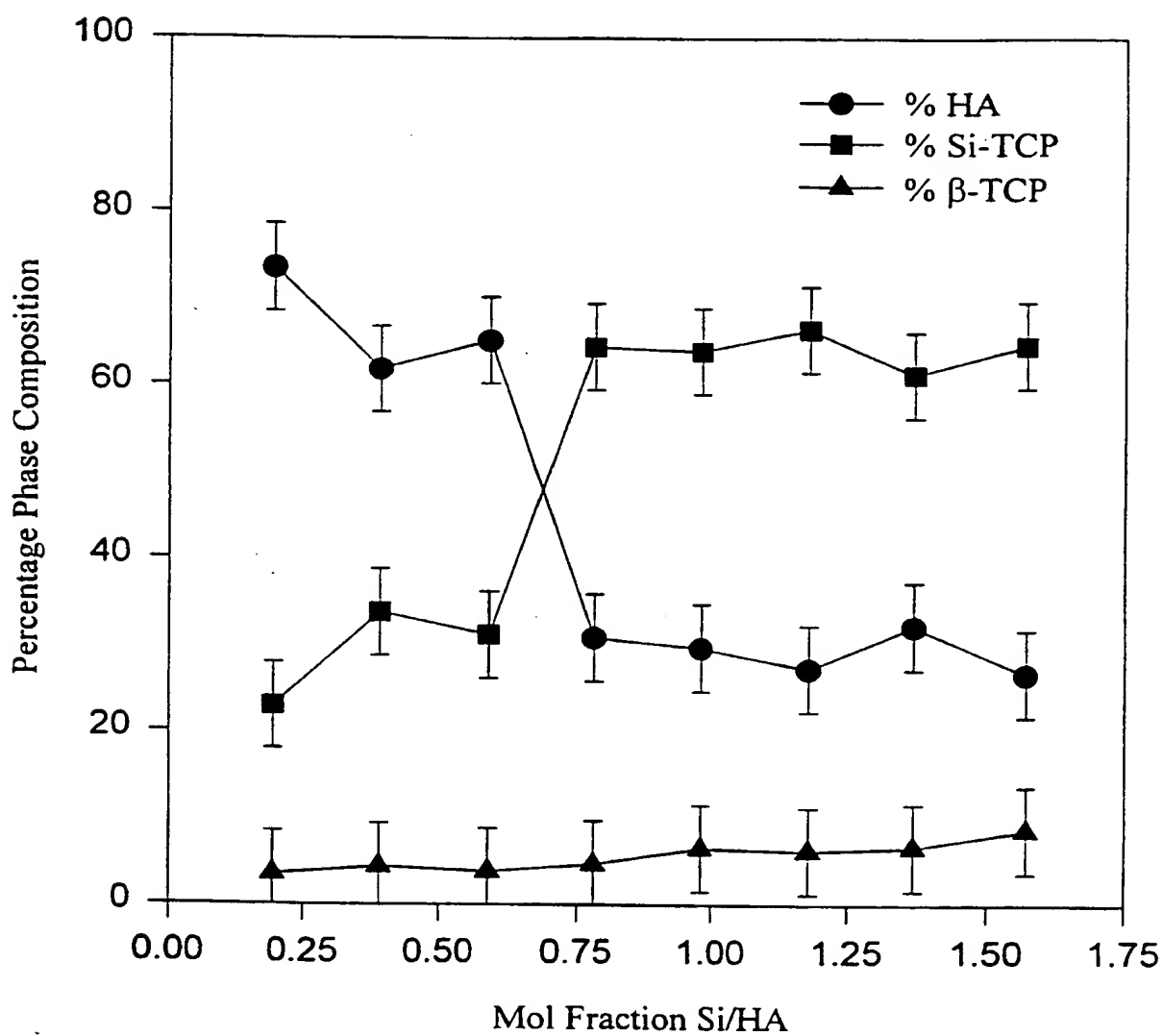


FIGURE 11

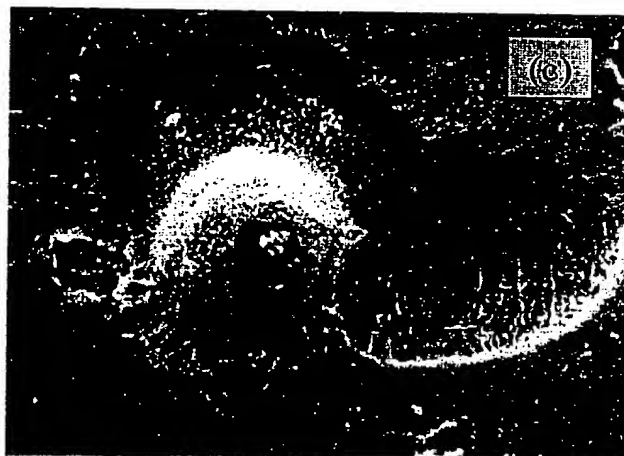
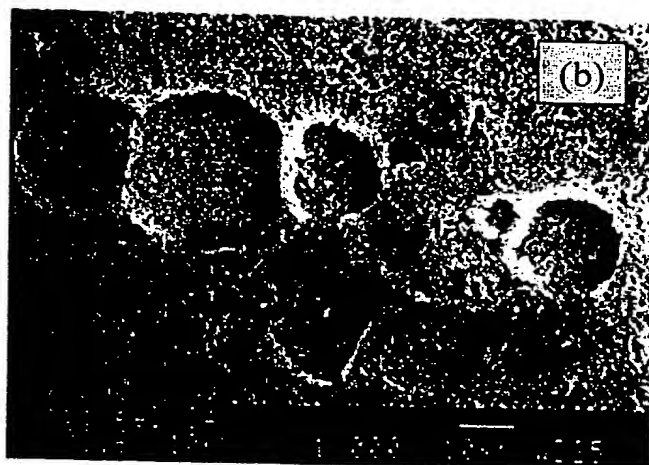
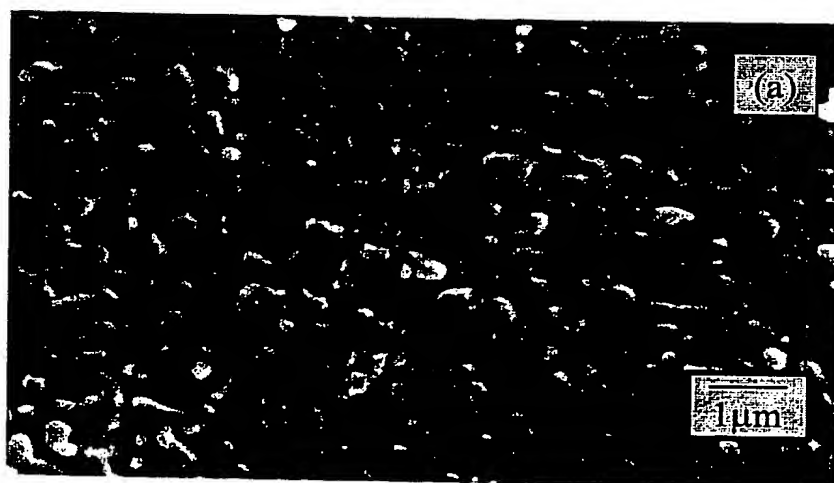


FIGURE 12

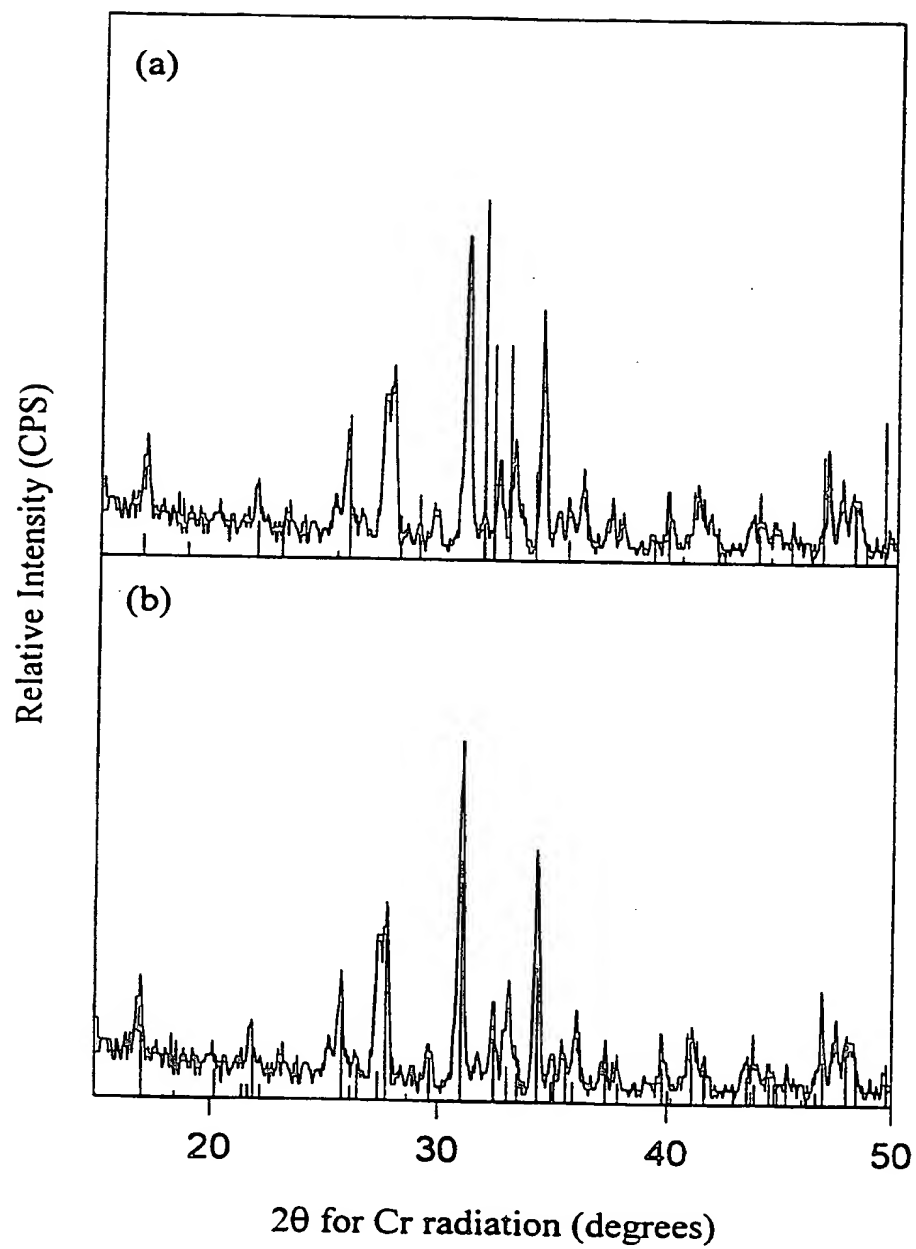


FIGURE 13

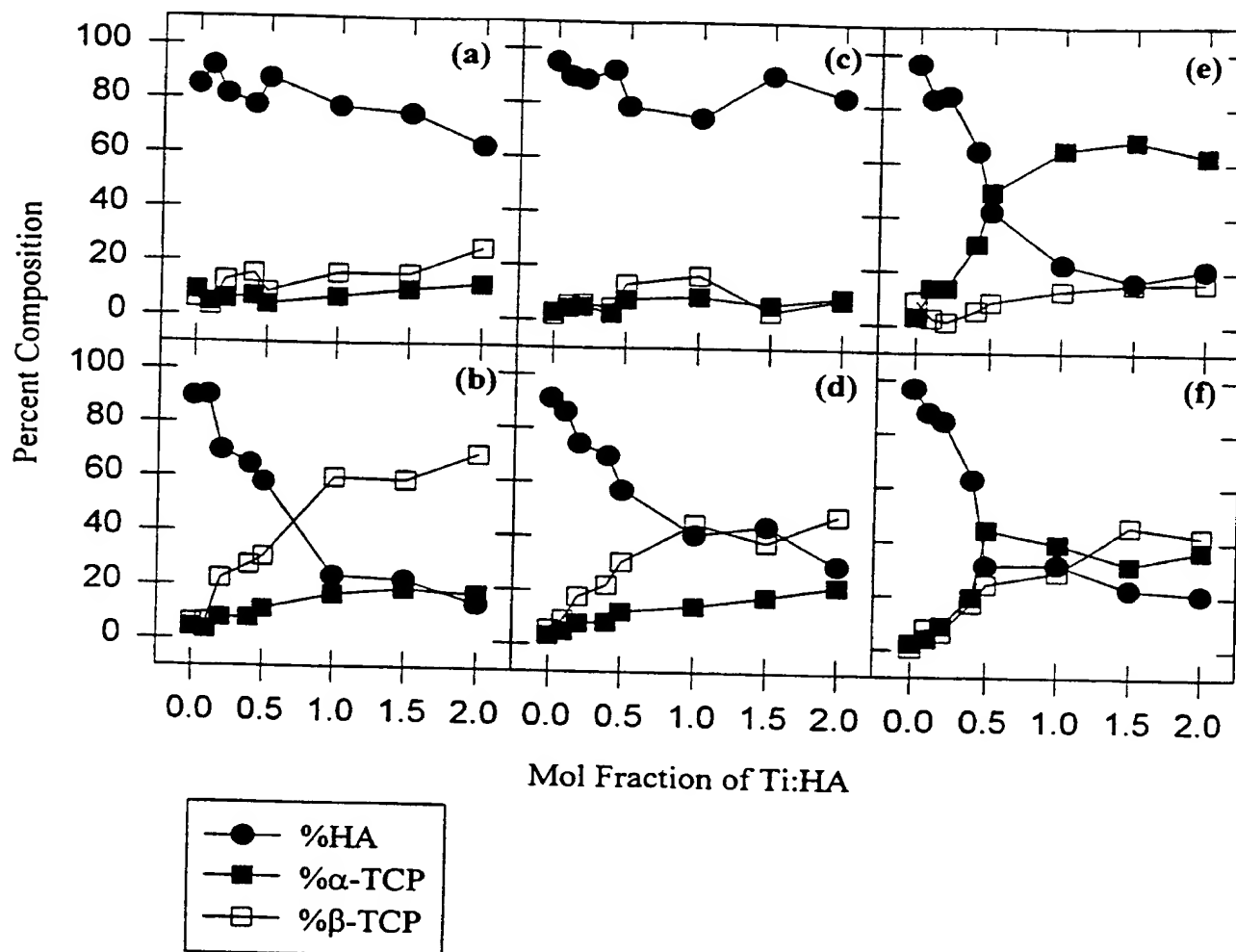


FIGURE 14

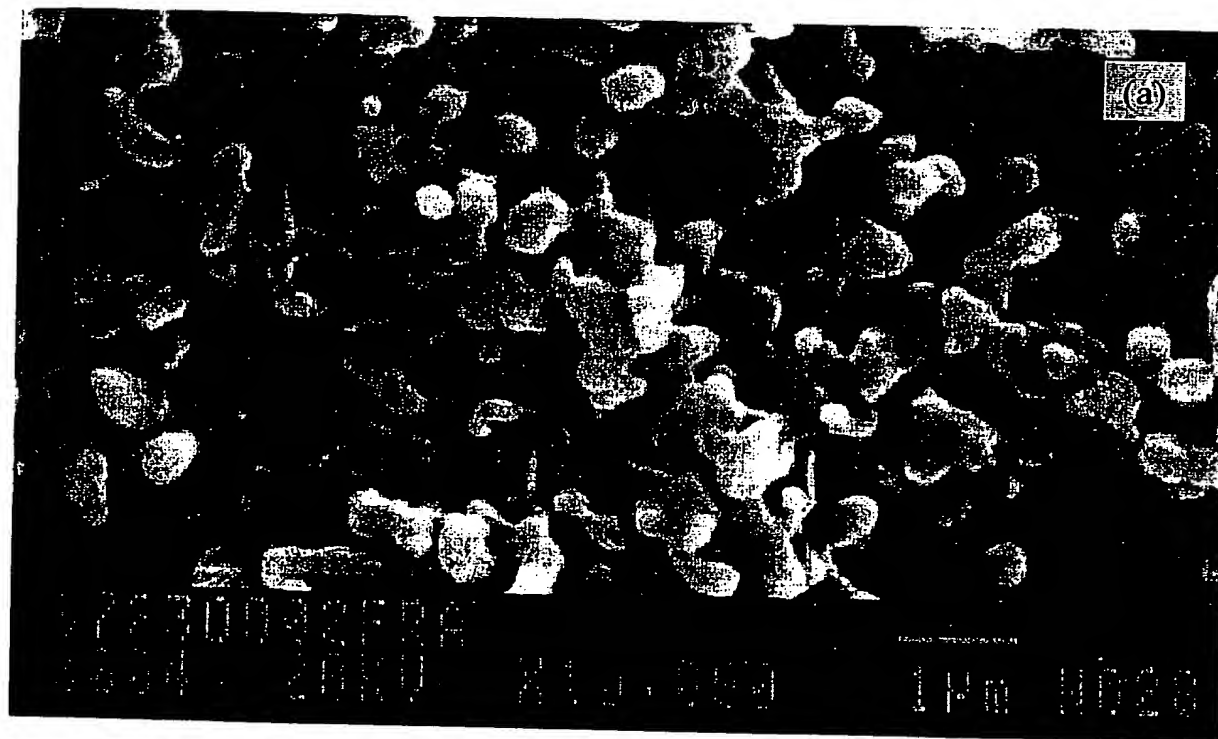


FIGURE 15

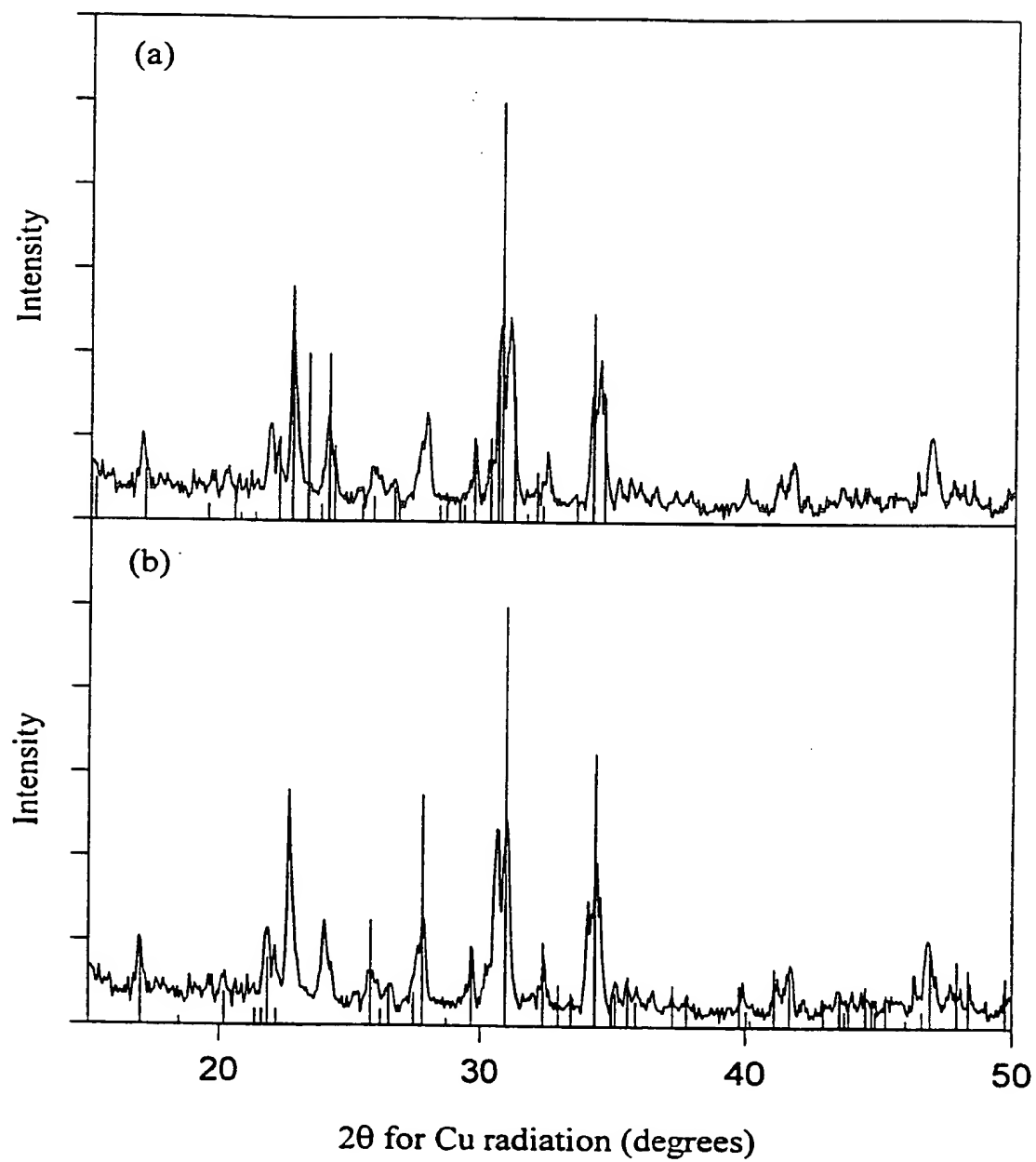


FIGURE 16

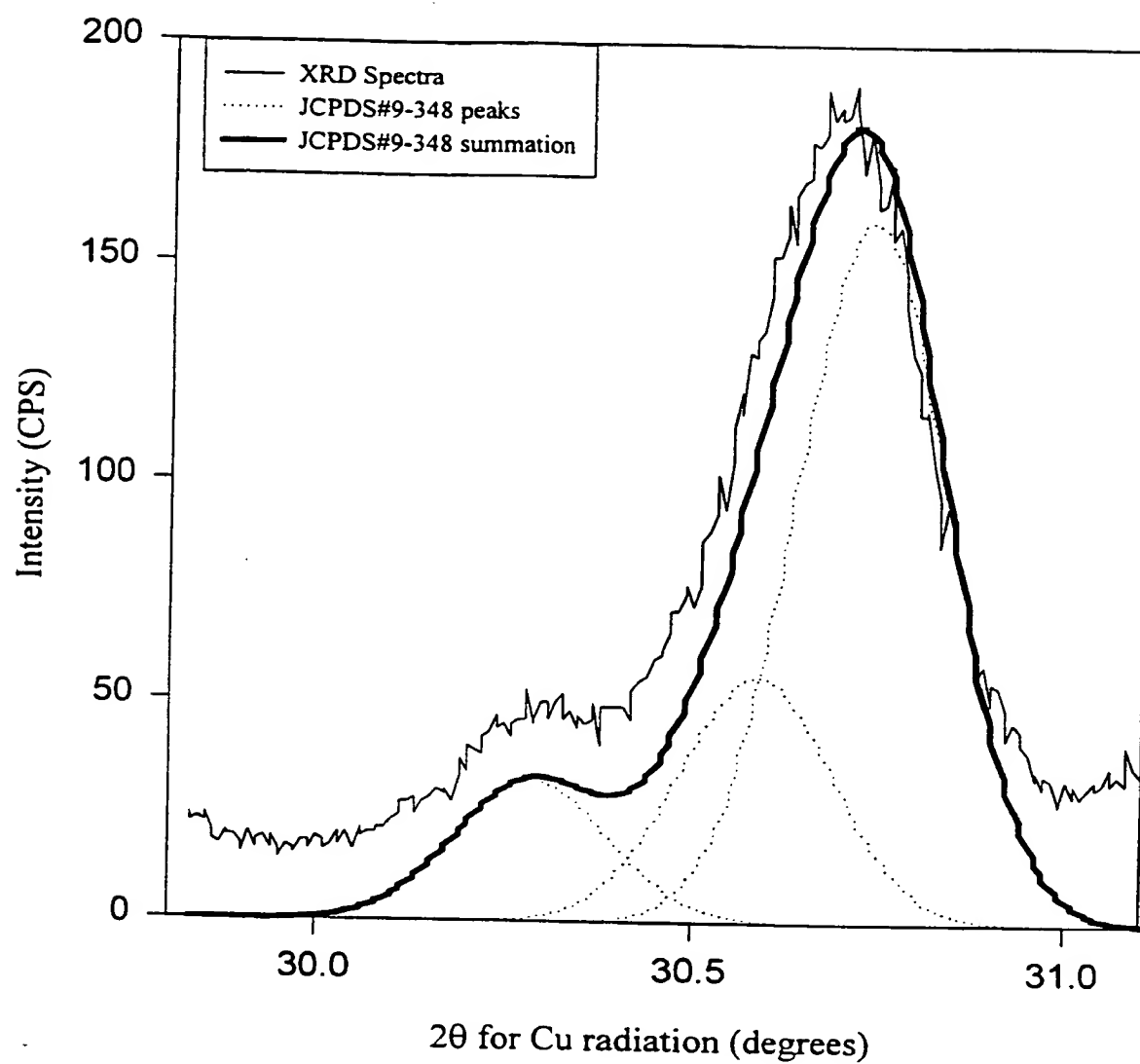


FIGURE 17

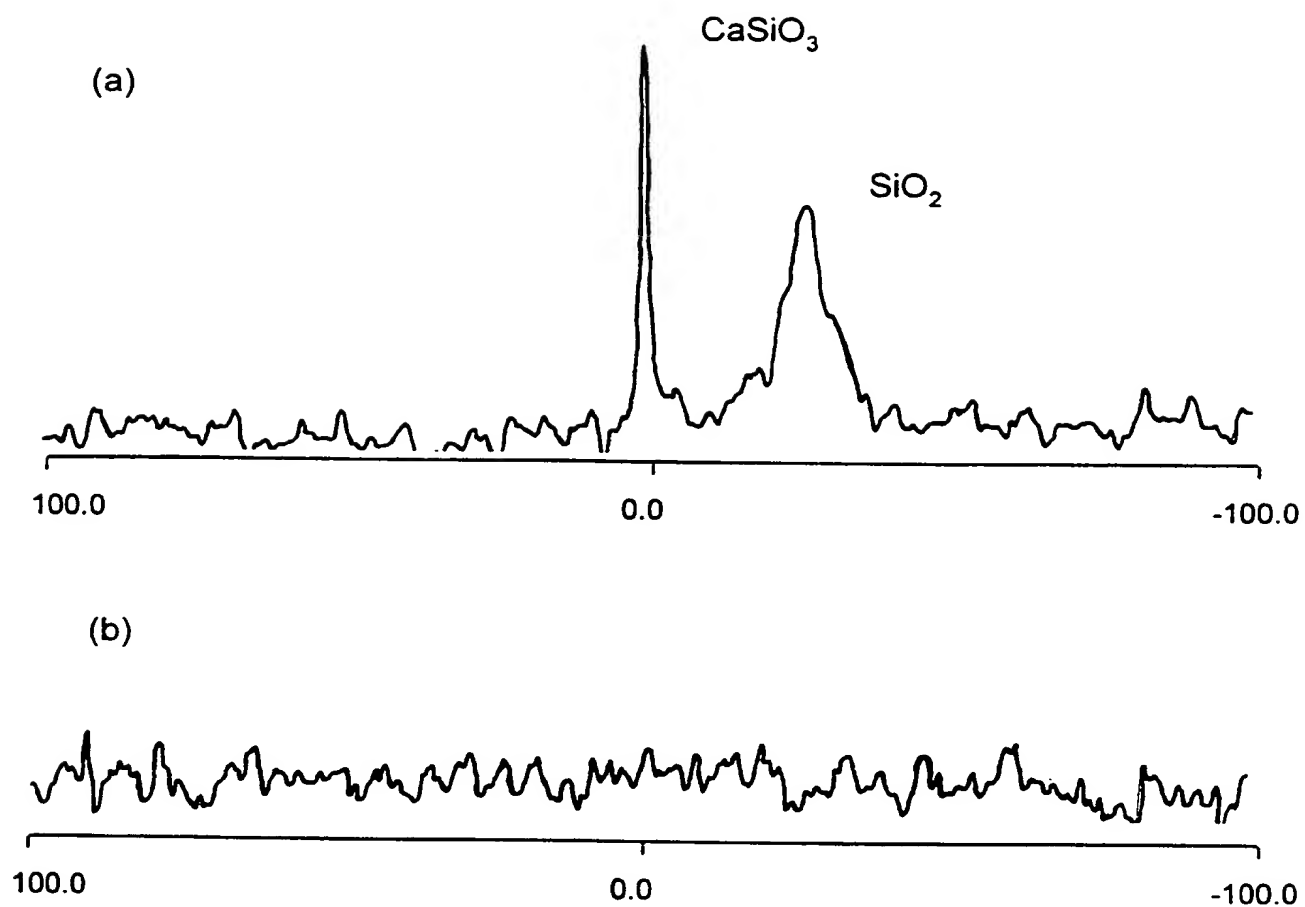
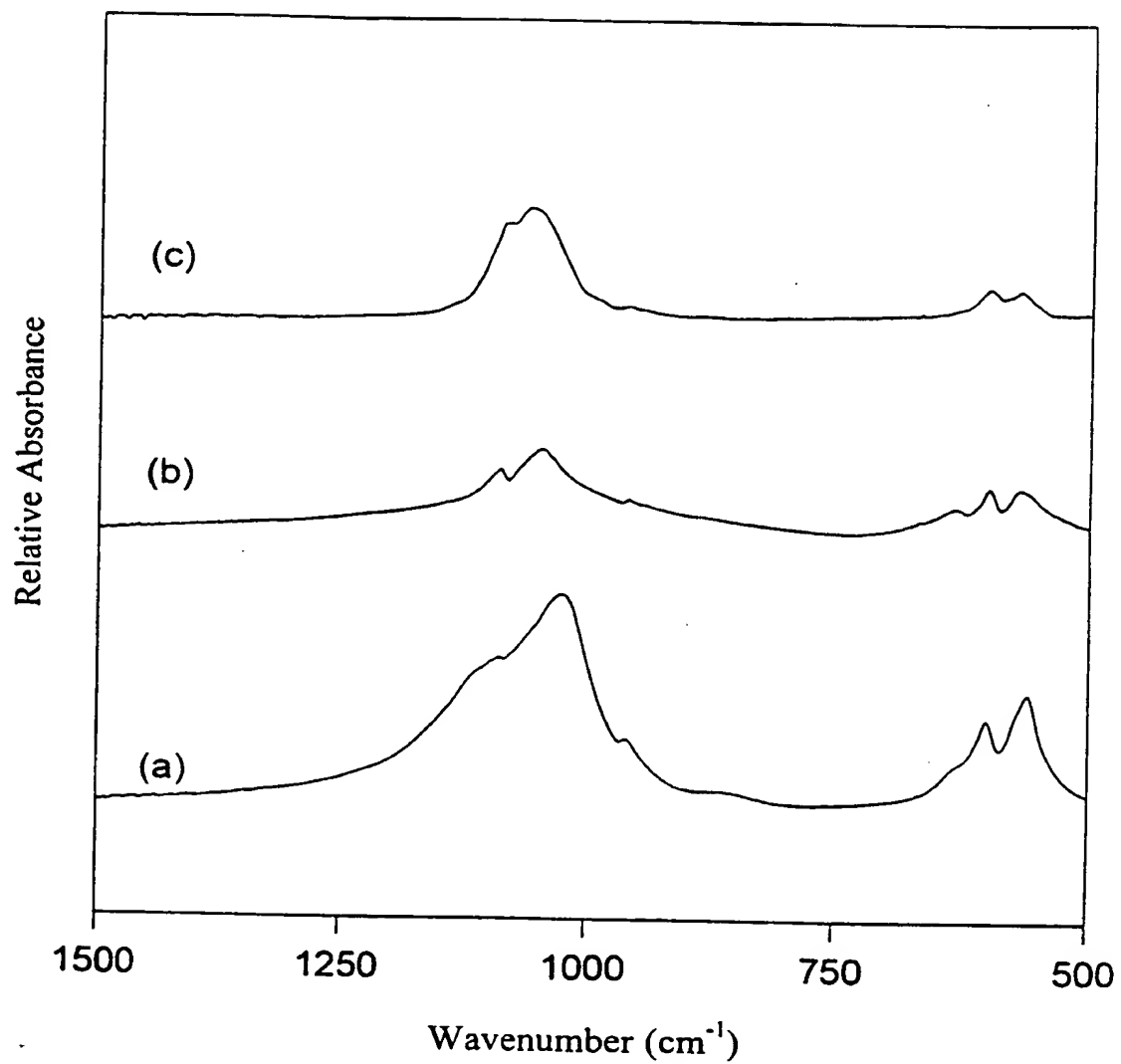


FIGURE 18



19 / 19
FIGURE 19